Report on Implementation of Post-Approval Studies for Medical Devices Workshop

June 4-5, 2009
FDA White Oak Conference Center
10903 New Hampshire Avenue
Silver Spring, MD 20993

Division of Epidemiology
Office of Surveillance and Biometrics
Center for Devices and Radiological Health
Food and Drug Administration

Report Date: November 30, 2009

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Executive Summary

The Division of Epidemiology (DEPI), Office of Surveillance and Biometrics (OSB), in the Center for Devices and Radiological Health (CDRH), believed that it was important to have an open dialogue with those directly or indirectly involved in collecting and analyzing data relevant to estimating medical device use and risk and in communicating risk to target populations as it relates to post-approval studies (PAS).

Accordingly, CDRH/OSB/DEPI hosted a two-day public workshop entitled "Implementation of Post-Approval Studies for Medical Devices." The workshop was held June 4-5, 2009 at FDA's conference center at Silver Spring, Maryland. The workshop was designed to engage industry and other stakeholders on topics related to the successful implementation of PAS.

The workshop brought together a diverse group of participants from various organizations including manufacturers, regulators, scientists, and administrators to exchange ideas focused on learning and improvement of implementation strategies for PAS. The workshop was attended by 131 participants. An additional 42 people participated via a webcast.

In the morning of day 1 of the workshop, there were two sessions, the first on "Challenges in Patient Recruitment and Retention in Post-Approval Studies" and the second on "Further Considerations in Implementing Post-Approval Studies." Short presentations were given by industry, Contract Research Organization (CRO) representatives, clinical trial consultants, and government representatives. The speakers provided their prospective on topics including the patient perspective on participating in clinical trials, site issues related to recruitment and retention, and IRB considerations in implementing PAS.

In the afternoon of day 1 of the workshop, attendees participated in break-out-sessions designed to encourage all attendees to present their views on barriers and opportunities for the recruitment and retention of participants in PAS.

Day 2 of the workshop consisted of discussing the critical issues identified and the highlights of the each of the breakout group sessions from day 1.

Day 2 of the workshop also included a panel discussion that focused on identifying priorities and next steps. Panelists from industry, NIH, and FDA's Office of Device Evaluation (ODE), Office of Compliance, and OSB answered audience questions, which included applying the "Total Product Life Cycle" approach to evaluating device performance, issues related to obtaining IRB approvals, and methodological approaches to address relevant postmarket and public health questions.

I. Background

One of CDRH's most important roles in carrying out its public health mission is to monitor and evaluate the safety and effectiveness of medical devices postmarket. Within CDRH, OSB is charged with implementing programs and surveillance activities to monitor the safety and effectiveness of medical devices approved for marketing or already commercially in use.

One particular program under the purview of OSB is the PAS program. In January 2005, responsibility for oversight of PAS program was officially transferred from ODE to OSB. A PAS is a postmarket clinical study designed to gather specific information to address precise study objectives about an approved medical device. More specifically, evaluation of premarket approval applications (PMAs) involves CDRH evaluating the premarket information to reach a final decision on whether a product can be approved for marketing. To help assure the continued safety and effectiveness of an approved device, CDRH may require the sponsor to conduct a PAS as a condition of approval of their PMA under 21 CFR 814.82(a)(2), which states:

> *"Post-approval requirements may include as a condition to approval of the device: Continuing evaluation and periodic reporting on the safety, effectiveness, and reliability of the device for its intended use. FDA will state in the PMA approval order the reason or purpose for such requirement and the number of patients to be evaluated and the reports required to be submitted."*

For a PAS to be most effective, they must be well-designed, scientifically sound, meaningful and feasible, and they must provide complete and timely information. CDRH believed that it was important to have an open dialogue with those directly or indirectly involved in collecting and analyzing data relevant to estimating medical device use and risk and in communicating risk to target populations. The workshop was designed to engage industry and other stakeholders on topics related to PAS.

Accordingly, CDRH/OSB/DEPI hosted a two-day public workshop entitled "Implementation of Post-Approval Studies for Medical Devices." The workshop was held June 4-5, 2009 at FDA's conference center at Silver Spring, Maryland. The agenda of the meeting is presented in Attachment A. The workshop was designed to engage industry and other stakeholders on topics related to the successful implementation of PAS.

The workshop brought together a diverse group of participants from various organizations including manufacturers, regulators, scientists, and administrators to exchange ideas focused on learning and improvement of implementation strategies for PAS. The workshop was attended by 131 participants. An additional 42 people participated via a webcast.

II. Process

The *Implementation of Post-Approval Studies for Medical Devices* workshop was developed as follow-up to the PAS Meeting on May 10-11, 2007. The notice for the workshop was published in the Federal Register on May 6, 2009 (Attachment B), and information on the on workshop was also made available on the FDA website at http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/default.htm.

Holding these meetings is consistent with Section 406(b) of the Food and Drug Administration Modernization Act, which charges FDA with consulting with "appropriate scientific and academic experts, health care professionals, representatives of patient and advocacy groups and the regulatory industry" when developing its plans for statutory compliance with the law. CDRH does not seek advice or consensus at such meetings, but the staff looks for opinions from invited individuals on an ad hoc basis. Once CDRH develops its specific plans regarding the monitoring of medical devices, it will seek to obtain broad public input on this issue.

Specific planning for the meetings was conducted by Social and Scientific Systems. Organizations and individuals known to have a professional interest and expertise in the implementation of PAS were invited to participate in the workshop. Names of potential speakers and panelists representing industry were identified by AdvaMed. An invitation letter was sent to speakers and panelists (Attachment C).

The list of attendees at the meeting can be found in Attachment D and those who participated by phone can be found in Attachment E.

III. Summary of Meeting

A. Opening Remarks

Opening remarks for the *Implementation of Post-Approval Studies for Medical Devices* workshop were given by: Dr Dan Schulz, Director, CDRH; Dr. Markham Luke, Deputy Director, Office of Device Evaluation; and Dr. Susan Gardner, Director, OSB. Participants were welcomed and encouraged to share their opinions and expertise. Dr. Gardner discussed the FDA as a public health agency. She quoted a soon to be published commentary by Drs. Margaret Hamburg and Joshua Sharfstein.

> *"The FDA must make difficult decisions in the absence of ideal information. For medical products, the FDA Amendments Act of 2007 strengthened the agency's ability to place restrictions on the use of medications at the time of approval while requiring that additional safety data be gathered. These tools allow the FDA opportunities to change the regulatory oversight of products as they move from limited use in clinical trials to adoption in the medical system. The ability to detect and act on safety signals quickly can give an additional layer of confidence to support earlier approval of important medications. Transparency is a potent element of a successful strategy to enhance the work of the FDA and its credibility with the public. When ever possible, the FDA should provide the data on which it bases its regulatory decisions and other guidance and explain its decision-making process to the public."*

B. Workshop Goals

Dr. Danica Marinac-Dabic, Director, DEPI, discussed the workshop goals. The purpose of the public workshop was to facilitate discussion among FDA and other interested parties on issues related to the conduct of PAS for medical devices.

It was CDRH's desire to ensure that there is an ongoing, open dialogue between CDRH, industry, and other stakeholders regarding the success of the PAS program. The workshop gave the opportunity for participants to identify best practices, and identify opportunities for improvement. There was an opportunity for FDA to hear from industry and for CDRH to present their current thinking on the implementation of PAS.

The goal of this two-day workshop was to create a constructive and productive dialogue that would benefit the public health through higher quality PAS.

C. Challenges in Patient Recruitment and Retention

In the morning of day 1 of the workshop, there were two sessions; the first session was on challenges in patient recruitment and retention in PAS." Short presentations were given by industry, Contract Research Organization (CRO) representatives, clinical trial consultants, and government representatives. The speakers provided their prospective on topics including the patient perspective on participating in clinical trials, site issues related to recruitment and retention, and IRB considerations in implementing PAS. The presentations and spearker bios are include in Appendices F and G, respectively. Below are some of the key points made by each of the speakers. Please refer to the presentations for more details.

Todd Fonseca of Medtronic presented the industry perspective on patient recruitment.

- The highest recruitment rates in PAS are seen in studies where the design is align with standard practice. Deviations from standard practice may make it more difficult to recruit patients.

- The further from standard practice, the higher the potential impact on recruitment. The key issues that may impact recruitment include:
    - Potential that participants may be randomization to control group
    - Frequency of follow-up may be a disincentive. In clinical practice, some therapies do not require any follow-up procedures or assessments as a part of standard practice.

- There may be little or no incentive for patients to participate in PAS. There needs to be an incentive for patients to take on additional burden of procedures or in some cases wait for treatment when they can receive device commercially.

- There also may be a lack of interest from clinicians to enroll patients in PAS.

- There also is confusion about PAS from payor and IRBs. There needs to be clear guidance to IRBs and payor on product status.

- In addition, there is concern form industry that the cost of funding a PAS will be greater that the revenue generated by the product.

Danica Marinac-Dabic from the FDA, discussed challenges, and opportunities related to PAS for medical devices.

- There have been several improvements in PAS. The FDA PAS website (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/PMA_pas.cfm) allows for the tracking of PAS elements, including the study status.

- CDRH believes that PAS need to be meaningful and answer specific research questions and that industry, health professionals, and consumers all have an interest in knowing how these products perform in the real world.

- Participants were reminded that PAS are ordered as a condition of approval for a variety of reasons, such as:
    - gathering postmarket performance data that were not obtained during the premarket review process
    - Longer-term performance including effects of re-treatments and product changes
    - Real-world device performance in a broader population of patients and clinicians
    - Evaluation of the effectiveness of training programs
    - Studying devices in diverse populations and evaluate sub-group performance
    - Evaluation of the safety and effectiveness outcomes of concern
    - Balancing premarket burdens and learning from previous device for next generation devices.

- The major goals of the PAS program transformation were to enhance the scientific rigor of PAS, establish accountability for PAS commitments, and to increase transparency with the public.

- The vision for the post-approval study program includes:
    - Ensuring that important postmarket questions are addressed
    - That studies are founded on good science, are timely and provide useful results
    - That existing external databases infrastructure are explored and utilized when appropriate
    - That stakeholders are kept apprised of status of PAS
    - collaboration is stressed throughout the product life cycle.

Christine K. Pierre of RxTrials, Inc. presented the site perspective on patient recruitment.

- She presented information from Site Solutions Summit Survey 2009, which surveyed investigators on participating PAS. The survey indicated that:
    - Investigators felt there was a decrease return on investment for participating in these studies
    - There was diminished scientific interest in PAS compared to pre-market trials
    - That investigators felt that sites were selected by marketing division versus the research division and that they were told this is a "prelude" to getting "more studies"
    - In some cases, participating in the study was the only way to get paid for the use of the product
    - Some novice investigators participated in PAS to build their CV for future research
    - That some investigators felt PAS were a filler until "real studies" become available.

- She also stated that the site and investigator's interest has a large impact on patient recruitment. In a recent survey, only 7% patients reported that they have ever been suggested by their doctors that they participate in studies.

David Rutledge of Abbott Vascular presented the industry perspective on patient retention.

- General Issues Related to PAS
    - For both IDE trials and PAS, it is important to have quality sites and trained staff.
    - Infrastructure needed is needed for a successful site. The infrastructure needed varies by number of cases involved.
    - There must be a budget in place for the study. If this is a research, companies should pay.
    - It is unclear how much monitoring should be done of PAS. Guidance is needed on what level of monitoring is appropriate.
    - There is currently a great pressure to outsource the conduct of studies.

- Patient Retention
    - To improve patient retention protocol should have an extended visit window, to minimize protocol deviations and have follow-up correspond with standard of care visits, if available.
    - To make it easier to reach participants, sites should obtain multiple contact numbers from patients.
    - A panel discussion on patient retention could be included as part of the Investigator/Coordinator meetings.

- Investigators should emphasize the additional benefits to patients of being in the study (more visits/calls, personal attention). Make patients aware of any compensation that is available for participating in the study.
- Investigators/Coordinators should demonstrate the value of their participation. This could include things such as providing information patients needs that may not be related to the study.
- Schedule alternative clinics for follow-up of study patients, making it more convenient for them to make the scheduled visits.

- Site Selection and Performance
  - Increase payment to a site may not improve a site's performance.
  - Sponsors should ask for long term follow-up rates from pervious studies in evaluating potential sites past experience and what other trials the site is conducting.
  - Performance-based program may lead to better performance. This could include rewarding coordinators. One should not underestimate of focusing on coordinators. This could include forming a coordinator network and having regular teleconference with coordinator and investigators.

Nancy Dianis, of Westat presented the Contract Research Organization (CRO) perspective on patient retention. She outlined three guiding principals for participant retention.

- Reducing the barriers to participation by selecting study sites and hours that are convenient to patients. Reimbursement for expenses such as travel and dependent care reduce the financial barrier to participation.

- Inspiring participation can mean gearing the recruitment and retention message for a specific gender, age, culture, or disease.

- Having good first response increases the likelihood of long term retention. An active follow-up system with current accurate contact information that utilizes tracking systems can maximize retention rates.

Paul Goebel, Paul W. Goebel Consulting Inc discussed IRB considerations in implementing PAS.

- The current guidance on PAS does not mention IRBs. It would be very helpful to have a guidance document from FDA that addresses IRB issues related to the conduct of PAS.

- IRBs need to have clear definition of PAS. IRBs need to know that PAS are not conducted under the IDE regulation since, by definition, the device in a PAS has already been approved for marketing by PMA

- The information required for IRB is not outlined in the approval order. If a device is approved for use, it would be helpful if could provide additional information that would be helpful to the IRB in its review. It would help IRBs to know what FDA's concerns about requiring a PAS.

- The use of centralized IRB may decrease the start up time needed for PAS. They should be considered when possible.

D. Other Considerations in Implementing Post-Approval Studies

In the afternoon of day 1 of the workshop, the sessions on "Further Considerations in Implementing Post-Approval Studies" short presentations were given by industry, CRO representatives, clinical trial consultants, and government representatives. The speakers provided their prospective on topics including site issues related to recruitment and retention, and legal considerations in implementing PAS. The presentations and spearker bios are include in Appendixes F and G, respectively. Below are some of the key points made by each of the speakers. Please refer to the presentations for more details.

Diane Simmons of the Center for Information and Study on Clinical Research Participation presented a summary of the current attitudes regarding on clinical research and what opportunities for improvement are available.

- She indicate that research has shown that 70%-83% of Americans believe clinical research is 'very important' or 'essential' to advancing public health. However, 42% of Americans distrust biopharmaceutical companies; only 14% believe they are 'honest' to public (similar rating for tobacco, oil & used car sales industry). Only 31% of Americans believe the FDA is effective at ensuring public/patient safety and 25% of Americans believe that Principal Investigators (PI) and study staff are solely motivated by greed. This research shows that public trust is getting in the way of people recognizing and enrolling in clinical trials.

- Public education and outreach impact not only long term awareness and support but also short term recruitment and enrollment rates. A variety of organizations – patient advocacy groups, investigative sites, government agencies, sponsors, and CRO companies - are implementing a public service campaign and other public education and outreach initiatives.

- Recruitment efforts should take advantage of the growing use of social networks and online listings/registries. This includes commercial social networking sites (e.g., Facebook), social networking and registries through patient advocacy groups, and the clinical research volunteer community on www.medhero.org.

- Outreach and education can address challenges in patient recruitment and retention. This could include:
  - PSAs
  - Media Outreach
  - Public Polls
  - Grassroots Education
  - Books
  - Brochures
  - DVDs
  - Newsletters
  - Website/Web Search Tool
  - Social Networks

- Community Building
- Science Museums
- High School & Middle School Initiatives.

Steven Pashko of Global Late Phase Studies, Omnicare Clinical Research discussed recruitment of clinical sites for PAS.

- The general site requirement should include, adequate and qualified clinical research staff available for the duration of the study, adequate procedures, facilities and equipment, the ability to recruit a specified number of subjects within the recruitment timeline, the ability to complete required documentation within a reasonable time frame, and a lack of competing studies that might thwart enrolment.

- There are a number of sources available to identify potential sites, including medical directories, professional associations, research literature, and commercial databases. Sponsor's listings of past investigator, and CRO investigator recruitment databases.

- There are some common reasons that studies fail. These include:
  - Designing a study that is infeasible
  - Recruiting sites that may not be able to conduct the study
  - Study death due to slow enrollment
  - Lack of timely start-up, which includes delays due to haggling about finances and legal wording in the contract
  - Non-administrative delays, such a IRB approval.

John J. Smith of Hogan and Hartson, LLP, discussed legal consideration of PAS.

- Legal Authority by which PAS can be imposed:
  - Section 513(a)(3)(C) of the Federal Food, Drug, and Cosmetic Act (FDC Act) (21 U.S.C. § 360c(a)(3)(C))
  - The Food and Drug Administration Modernization Act (FDAMA)
  - Post-approval requirements regulations at 21 C.F.R. § 814.82(a)

- The PAS approval process. He stated that CDRH and sponsor should agree on protocol for post-approval study at the time of approval. However, if no agreement can be reached prior to PMA approval, sponsor should submit the study protocol as a PMA supplement within 30 days of PMA approval. FDA is expected to act on and respond to the protocol submission within 60 calendar days of receipt. If an agreement on a protocol cannot be reached, FDA may use its authority to order postmarket surveillance under section 522 of the act (21 U.S.C. § 360l; 21 C.F.R. Part 822).

Solomon Iyasu, Director the CDER/OSE, discussed common considerations in implementing PAS in devices and drugs.

- The limitations of the pre-market clinical trial safety evaluation.

- Sources of post-market safety data.

- Key challenges of observation epidemiologic database studies.

- Key challenges in using registry data.

- The implication of FDAAA, the enhanced authorities regarding postmarket safety of drugs.

E. Break-out Session

In the afternoon of day 1, the workshop were broken into two group to discuss what discuss what was learn at the sessions and to identify what were the critical issues in implementing PAS. Breakout group 1 was led by Ellen Pinnow of CDRH and Libby Cerullo of Stryker Spine. Group 2 was led by Daniel Canos of CDHR and Heidi Hinrichs of St. Jude Medical. The groups met separately and discussed the questions on the list (Appendix H). In the morning of day 2, a summary of discussions were presented by the combined group participants. Below are the collective issues identified by the breakout groups.

A discussion of factors that impact site recruitment.

- Participants indicated that the level of interested in the product plays a large role in the interest of a site participating in a PAS.

- The market position of a device may impact if sites are willing or able to participate in a PAS for a particular device. A PAS for a device may be competing with novel technology or other studies enrolling the same patient population.

- There was a discussion of how to create interest in participating in PAS. There is additional work of having to complete case report forms. Sites are also following a protocol and standard of care consideration. Involving site investigators in publications may be a strategy to increase interest.

- It was suggest that interest in PAS may be increased by incorporating site specific research interest into the PAS.

- There may be more interest in participating in PAS if they studies provided class I evidence to support reimbursement

- Industry representatives were also concerned about the cost of conducting PAS and the return on investment for these studies

A discussion of IRB issues and opportunities.

- Participants indicated that increased distribution and visibility of CDRH's IRB letter would help in increasing awareness of IRB requirements for PAS and possibly decrease the time to approval. The content of this includes explanation on PAS and use of central of IRBs.

- There is a need for outreach and education for IRBs regarding PAS.

- There is a needed for additional guidance for IRBs regarding review of PAS. This could be done via websites that provide information on PAS targeting IRBs.

- Participants indicated that it would be helpful to have an letter explaining reason and conditions of PAS created/approved along with PAS protocol that could be presented to the IRB.

- The IRB need to assesss fair market value to ensure no coercion to participate in a study.

- IRB requirements to disclose investigator financial relationships in informed consent

- Participants emphasized that PAS can use a centralized IRB. Use of a Centralized IRB is useful when a study has multiple sites. In many cases, centralized IRBs are more expeditious

A discussion of patient recruitment.

- To increase patient enrollment, a PAS should be designed with a with broad inclusion/exclusion criteria. There are some issues associated with having a all comers study. This includes the concern that including off-label use and patients with contraindications may be viewed as a compliance issue.

- It was suggested that borrowing patients from the IDE study to support the PAS when possible. This includes borrowing patients from the PAS to support the long term follow-up of the IDE study when possible.

- Most important factor in patient recruitment is the research coordinator. It is best to try to minimize the research staff turnover rate as training new staff is expensive and labor intensive.

- Recruitment success is based on the site's relationship with patient and gaining patient trust.

- It was suggested that it would be helpful to have Public Service Announcements encouraging patients to participate in study. This could include targeting messages for the expanded population. It would also be useful to have information on the web regarding PAS.

A discussion of patient retention.

- It was suggested that increases time windows for follow-up would increase patient retention rates.

- There needs to be a clear definition of what is classified as lost to follow-up. If a patient misses two visits in a row should they be considered lost to follow-up or is this an issue of non-compliance with study visits.

- It is expected that there would be different retention rates for captive versus non-captive patients. One should consider the patient population when designing retention strategies.

- Keeping patients informed of study progress along the way also helps with retention. Sending birthday cards, newsletters, etc. help keep patients engaged in the study.

F. Workshop Panel Discussion

Robert Ciperson of CDRH moderated the workshop panel session on day 2. The panel included FDA, NIH, consultants, and industry representatives. The workshop panel included:

- Danica Marinac-Dabic, OSB
- Thomas Gross, OSB
- Malvina Eydelman, ODE
- Mark Melkerson, ODE
- Bram Zuckerman, ODE
- Michael Marcarelli, Office of Compliance (OC)
- Michael Domanski, NIH/NHLBI
- Paul Goebel, Goebel Consulting
- Stan Harris, Wright Medical Technology
- Jing Xie, Biomet Manufacturing.

A list of the questions for the workshop panel discussion is included in Appendix I.

The workshop panel members discussed the processes that are currently in place to identify issues that may be appropriately addressed in a PAS. In addition, they made recommendation that would make study design negotiations between FDA and the sponsor more successful. It was suggested by audience participants that it would be helpful to have a guidance from FDA on how to determine if a PAS is needed and what elements should be included in the PAS. The workshop panel members agreed that FDA and the sponsor should determine the unanswered questions from IDE. In addition, there should be ongoing communication on the PAS between FDA and sponsor to address protocol modifications and practical issues encountered in the conduct of PAS.

The workshop panel member discussed ways that CROs, professional societies, and industry could be involved in designing PAS. The benefits of this involvement included the ability to identify data sources and employ innovative study designs. They strongly encouraged creativity when identifying source data. FDA encourages sponsors to leverage existing databases and consider Outside of US (OUS) data that can be used to support PAS.

The workshop panel also discussed issues related to the quality of data available in PAS. Members of the panel representing industry indicated that there was a lack of standards on quality of data and on a lack of guidance on monitoring requirements. FDA agreed that the current guidance document does not address monitoring requirements and that a guidance document on qualify of data and monitoring requirements is needed. Currently, the level of monitoring is based on risk.

Workshop participants also raised questions related to IRB considerations of implementing PAS. Participants would live to have a guidance document from FDA that addresses IRB issues related to the conduct of PAS. They also felt that it would be helpful if could provide additional

information that would be helpful to the IRB in its review. It would help IRBs to know FDA's concerns about requiring a PAS.

Workshop participants also raised the issue that there is some questions if having a all comers study is a appropriate choice for a PAS. There is concern that including off-label use and patients with contraindications may be viewed as a compliance issue.

IV. Conclusion of the Meeting

CDRH staff expressed their gratitude for the comments of all the participants, as well as their intent to follow up with many of the suggestions and concerns raised at the meeting. Issues identified included:

- There is need to include a link to CDRH's letter to IRBs on the PAS website.
- There is a need for IRB education and guidance related to implementation of PAS.
- There is a need for additional guidance on how to determine if a PAS is needed.
- There is a need for additional guidance on data sources that can be used to conduct PAS.
- There is a need for outreach to the clinicians and patients to increase awareness about PAS.

V. Accomplishments Following the Meeting

- The link to CDRH's letter to IRBs has been placed on the PAS website. The link can be found at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma_pas.cfm.
- DEPI is in the process of drafting a Post-Approval Study Criteria document that will be made available to stakeholders upon completion.
- DEPI has drafted a generic letter to investigators emphasizing the importance of compliance with scheduled follow-up visits. This letter can be utilized by sponsor's to highlight FDA's commitment to well executed PAS and encourage site compliance. A link to this letter has been placed on the PAS website.
- DEPI has drafted a generic letter to participants emphasizing the importance of compliance with scheduled follow-up visits. This letter can be utilized by clinical sites to encourage patient compliance. A link to this letter has been placed on the PAS website.
- DEPI held a workshop on Methodologies for Post-Approval Studies of Medical Devices. This workshop was held September 9-10, 2009 at the FDA White Oak Conference Center.
- DEPI is in the process of planning future public workshops designed to gather information and provide guidance for stakeholders on methodology, data sources, and implementation strategies related to PAS.

- DEPI will hold a public workshop on April 30, 2010, focused on the development of the Medical Device Epidemiology Network (MDEpiNet). The purpose of this workshop is to facilitate discussion among FDA and academic researchers with expertise in epidemiology and health service research on issues related to the methodology for studying medical device performance.

- Additional workshops are in the planning phase. This includes a workshops on methodology associated with PAS for diagnostic medical devices and considerations in planning and utilizing registries.

VI. List of Attachments

- ATTACHMENT A: Agenda
- ATTACHMENT B: Federal Register Notice
- ATTACHMENT C: Invitation Letter for Speakers
- ATTACHMENT D: List of Attendees
- ATTACHMENT E: List of Webinar Participants
- ATTACHMENT F: Presentations
- ATTACHMENT G: Speaker Bios
- ATTACHMENT H: Breakout Session Questions
- ATTACHMENT I: Workshop Panel Questions

ATTACHMENT A: Agenda

Implementation of Post-Approval Studies for Medical Devices
June 4-5, 2009
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Agenda

Day 1

8:00 am **Breakfast and Registration**

9:00 am **Welcome**
Daniel Schultz, MD, CDRH
Susan Gardner, PhD, CDRH/OSB
Markham Luke, MD, PhD, CDRH/ODE

9:15 am **Workshop Goals**
Danica Marinac-Dabic, MD, Ph.D, CDRH/OSB/DEPI

Challenges in Patient Recruitment and Retention:
Moderator: *Cara Krulewitch, PhD, CDRH/OSB/DEPI*

9:30 am **Industry Perspective on Patient Recruitment**
Todd Fonseca, Medtronics

9:50 am **Post-Approval Studies for Medical Devices: Challenges and Opportunities**
Danica Marinac-Dabic, MD, PhD, CDRH /OSB/DEPI

10:10 am **The Site Perspective on Patient Recruitment**
Christine K. Pierre, RN, RxTrials, Inc.

10:30 am **Question & Answer**

10:40 am **Coffee Break**

10:55 am **Industry Perspective on Patient Retention**
David Rutledge, PharmD, Abbott Vascular

11:15 am **CRO Perspective on Patient Retention**
Nancy Dianis, RN, MS, Westat

11:35 am **IRB Considerations in Implementing Post-Approval Studies**
Paul Goebel, Paul W. Goebel Consulting Inc

11:55 am **Question & Answer**

12:05 pm **Lunch Discussion**

Further Considerations in Implementing Post-Approval Studies:
***Moderator*:** *Hesha Duggirala, PhD, CDRH/OSB/DEPI*

1:00 pm **Where are we now, Where do we go from here?**
Diane Simmons, Center for Information & Study on Clinical Research Participation

1:15 pm **Recruitment of Clinical Sites for Post-Approval Studies**

Steven Pashko, PhD, Global Late Phase Studies, Omnicare Clinical Research

1:30 p m **Legal Consideration of Post-Approval Studies**
John J. Smith, MD, JD, Hogan and Hartson, LLP

1:45 pm **Drugs and Devices: Common Considerations in Implementing Post-Approval Studies**
Solomon Iyasu, MD, PhD, CDER/OSE

2:00 pm **Question & Answer**

2:10 pm **Break**

2:20 pm **Break-out-Sessions: Recruitment and Retention of Participants**

Session I Leaders: *Ellen Pinnow, MS, CDRH/OSB/DEPI and Libby Cerullo, Stryker Spine*

Session II Leaders: *Daniel Canos MPH, CDRH/OSB/DEPI and Heidi Hinrichs, St. Jude Medical*

4:45 pm **Summary of Day 1**
Danica Marinac-Dabic, MD, PhD, CDRH/OSB/DEPI

Day 2

8:00 am **Breakfast/Discussions**

9:00 am **Summary of Break-out Session and Discussions: *What have we learned: Identifying the critical issues***

Session I Leaders: Ellen Pinnow, MS, CDRH/OSB/DEPI and Libby Cerullo, Stryker Spine

Session II Leaders: Daniel Canos MPH, CDRH/OSB/DEPI and Heidi Hinrichs, St. Jude Medical

10:15 am **Break**

10:30 am **Panel Discussion: *Where do we go from here: Identifying priorities and next steps***
Moderator:Robert Ciperson, MPH, CDRH/OSB
Panelists:
Jodi Akin, MSN, Edwards Lifesciences
Malvina Eydelman, MD, CDRH/ODE/DONED
Michael Domanski, MD, NIH/NHLBI
Thomas Gross, MD, MPH, CDRH/OSB
Stan Harris, Wright Medical Technology
Danica Marinac-Dabic, MD, Ph.D, CDRH/OSB/DEPI
Michael Marcarelli, PharmD, MS, CDRH/OC/DBM
Mark Melkerson, MS, CDRH/ODE/DSORD
Jing Xie, PhD, Biomet Manufacturing Inc.
Bram Zuckerman, MD, CDRH/ODE/DCD

11:50 am **Summary Wrap-up**
Danica Marinac-Dabic, MD, PhD, CDRH/OSB/DEPI

12 noon **End of Workshop**

ATTACHMENT B: Federal Register Notice

interested in collaborative research directed toward molecular strategies for vaccine and antiviral development, and animal models of viral hepatitis C. For more information, please contact Dr. T. Jake Liang at 301–496–1721, *jliang@nih.gov*, or Ms. Patricia Lake at 301–594–6762, *lakep@mail.nih.gov*.

Dated: April 29, 2009.

Richard U. Rodriguez,

Director, Division of Technology Development and Transfer, Office of Technology Transfer, National Institutes of Health.

[FR Doc. E9–10410 Filed 5–5–09; 8:45 am]

BILLING CODE 4140–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2009–N–0664]

Implementation of Post-Approval Studies for Medical Devices; Public Workshop

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of public workshop.

The Food and Drug Administration (FDA) is announcing a public workshop entitled "Implementation of Post-Approval Studies for Medical Devices." The purpose of the workshop is to facilitate discussion among FDA and other interested parties on issues related to the implementation of Post-Approval Studies for medical devices.

Date and Time: The workshop will be held on June 4, 2009, from 9 a.m. to 5 p.m. and June 5, 2009, from 9 a.m. to 12 p.m. Participants are encouraged to arrive early to ensure time for parking and security screening before the meeting. Security screening will begin at 8 a.m., and registration will begin at 8:30 a.m. Please pre-register by May 28, 2009, using the instructions in this document.

Location: The workshop will be held at the FDA White Oak Campus, 10903 New Hampshire Ave., Silver Spring, MD 20993.

Contact Persons: Ellen Pinnow, Center for Devices and Radiological Health (HFZ–541), Food and Drug Administration, 1350 Piccard Dr., Rockville, MD 20850, 240–276–2373, e-mail: *ellen.pinnow@fda.hhs.gov*; or Daniel Canos, Center for Devices and Radiological Health (HFZ–450), Food and Drug Administration, 1350 Piccard Dr., Rockville, MD 20850, 240–276–2369, *daniel.canos@fda.hhs.gov*.

Registration: E-mail your name, title, organization affiliation, address, and e-mail contact information to Stephanie Zafonte at *SZafonte@s-3.com*. There is no fee to attend the workshop, but attendees must register in advance. The registration process will be handled by Social and Scientific Systems, which has extensive experience in planning, executing, and organizing educational meetings. Although the facility is spacious, registration will be on a first-come, first-served basis. Non-U.S. citizens are subject to additional security screening, and they should register as soon as possible.

If you need special accommodations because of a disability, please contact Ellen Pinnow (see *Contact Persons*) at least 7 days before the public workshop.

SUPPLEMENTARY INFORMATION:

I. Why Are We Holding This Public Workshop?

The purpose of the public workshop is to facilitate discussion among FDA and other interested parties on issues related to the conduct of Post-Approval Studies for medical devices.

II. What Are the Topics We Intend To Address at the Public Workshop?

We hope to discuss a large number of issues at the workshop, including, but not limited to:

- Regulatory requirements for implementing a Post-Approval Study for medical devices;
- Challenges and successful strategies for the recruitment of participants for Post-Approval Studies;
- Challenges and successful strategies for the retention and compliance with follow-up requirements of participants for Post-Approval Studies;
- Using existing infrastructure (e.g., national registries) to facilitate Post-Approval Studies; Using innovative strategies to facilitate Post-Approval Studies;
- Clinical research organizations, industry, academia, and other clinical trial consultant's perspectives on all of the previous issues related to implementing Post-Approval Studies for medical devices.

III. Where Can I Find Out More About This Public Workshop?

Background information on the public workshop, registration information, the agenda, information about lodging, and other relevant information will be posted, as it becomes available, on the Internet at *http://www.fda.gov/cdrh/meetings.html*.

Dated: April 29, 2009.

Daniel G. Schultz,

Director, Center for Devices and Radiological Health.

[FR Doc. E9–10426 Filed 5–5–09; 8:45 am]

BILLING CODE 4160–01–S

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Institute of Allergy and Infectious Diseases; Notice of Closed Meetings

Pursuant to section 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. App.), notice is hereby given of the following meetings.

The meetings will be closed to the public in accordance with the provisions set forth in sections 552b(c)(4) and 552b(c)(6), Title 5 U.S.C., as amended. The grant applications and the discussions could disclose confidential trade secrets or commercial property such as patentable material, and personal information concerning individuals associated with the grant applications, the disclosure of which would constitute a clearly unwarranted invasion of personal privacy.

Name of Committee: National Institute of Allergy and Infectious Diseases Special Emphasis Panel; Unsolicited Multi-Project Application.

Date: May 22, 2009.

Time: 11 a.m. to 2 p.m.

Agenda: To review and evaluate grant applications.

Place: National Institutes of Health, 6700B Rockledge Drive, Bethesda, MD 20817. (Telephone Conference Call).

Contact Person: Peter R Jackson, Ph.D., Scientific Review Administrator, Scientific Review Program, Division of Extramural Activities, NIH/NIAID/DHHS, 6700–B Rockledge Drive, MSC 7616 Room 2220, Bethesda, MD 20892–7616. 301–496–2550.

Name of Committee: National Institute of Allergy and Infectious Diseases Special Emphasis Panel; Ancillary Studies in Immunomodulation Clinical Trials.

Date: May 29, 2009.

Time: 2 p.m. to 4:30 p.m.

Agenda: To review and evaluate grant applications.

Place: National Institutes of Health, 6700B Rockledge Drive, Bethesda, MD 20817 (Telephone Conference Call).

Contact Person: Paul A. Amstad, PhD, Scientific Review Officer, Scientific Review Program, Division of Extramural Activities, NIAID/NIH/DHHS, 6700B Rockledge Drive, MSC 7616, Bethesda, MD 20892–7616. 301–402–7098. *pamstad@niaid.nih.gov*.

(Catalogue of Federal Domestic Assistance Program Nos. 93.855, Allergy, Immunology, and Transplantation Research; 93.856, Microbiology and Infectious Diseases Research, National Institutes of Health, HHS)

Dated: April 29, 2009.

Jennifer Spaeth,

Director, Office of Federal Advisory Committee Policy.

[FR Doc. E9–10422 Filed 5–5–09; 8:45 am]

BILLING CODE 4140–01–P

ATTACHMENT C: Invitation Letter for Speakers

May 6, 2009

Dear

FDA's Center for Devices and Radiological Health (CDRH) is hosting a two-day public workshop entitled **"Implementation of Post-Approval Studies for Medical Devices"**. The workshop will be held **June 4-5 at the FDA's Conference Center at Silver Spring Maryland**.

CDRH considers Post-Approval Studies (PAS) to be an important public health tool. In order for PAS to be most effective, they must be well-designed, scientifically sound, meaningful and feasible, and they must provide complete and timely information. CDRH believes it is crucial that industry is well informed and engaged in continuous dialogue regarding the post-approval studies. In addition, since the role of other public health partners is expanding as evident by a number of efforts external to CDRH that are directly or indirectly involved in collecting and analyzing data relevant to estimating medical device use and risk and in communicating risk to target populations, CDRH believes that they too need to be involved in dialogue.

During the past several years CDRH has made a significant commitment to enhance the Post-Approval Studies (PAS) Program. The Division of Epidemiology at CDRH's Office of Surveillance and Biometrics has assumed leadership of the Program to bring their unique expertise in the design of postmarket studies to the Program. CDRH epidemiologists are working closely with their premarket colleagues to ensure that the potential for a post-approval study is recognized early in the review process. Then, if the application is approved, an effectively designed study will be ready for implementation.

In addition to greater emphasis on proactive involvement and high-quality study design, CDRH has committed resources to a new automated tracking system that efficiently identifies the reporting status of all active post-approval studies. This system represents CDRH's determination to ensure that all post market commitments are fulfilled. The status of every study is posted on this website so that all stakeholders are kept informed of their progress and potential problems. CDRH has also created a guidance document to explain these organizational and systemic changes to all stakeholders.

It is the Center's desire to ensure that there is an ongoing, open dialogue between CDRH, industry and other stakeholders regarding the success of the PAS Program. This forum on Post Approval Studies will bring together representatives from various organizations including manufacturers, regulators, scientists, and administrators to exchange ideas focused on learning and improvement of implementation strategies for post-approval studies. CDRH is committed to listening to its stakeholders, identifying and building on best practices, and seizing any opportunity for improvement.

I would like to invite you to participate in this workshop event as a speaker on June _, 2009. Your participation will add great value to discussion and development of strategies to improve implementation of post-approval medical device studies. Date and time of your presentation is _____. Please register for the workshop by going online to https://medsun2.s-3.net/FDAPASWkshpJun09/. Travel costs for those coming from out of town

will be reimbursed and can be arranged by contacting Stephanie Zafonte at 1-800-859-9821 or by email at szafonte@s-3.com. Please direct any questions to Stephanie Zafonte as well.

We hope you will join us for two days of constructive and productive dialogue that will, if successful, benefit the public health through higher quality Post Approval Studies.

Sincerely,
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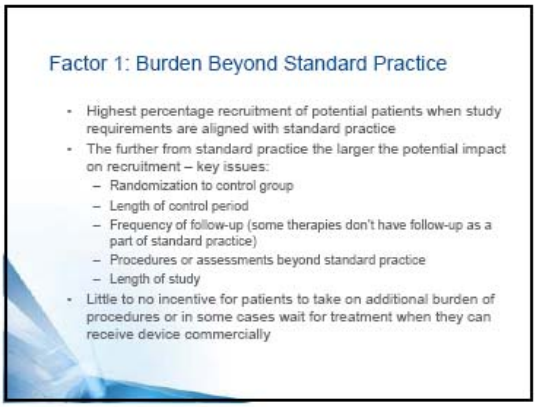
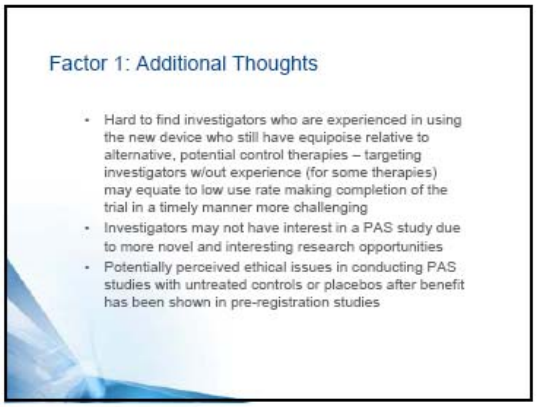
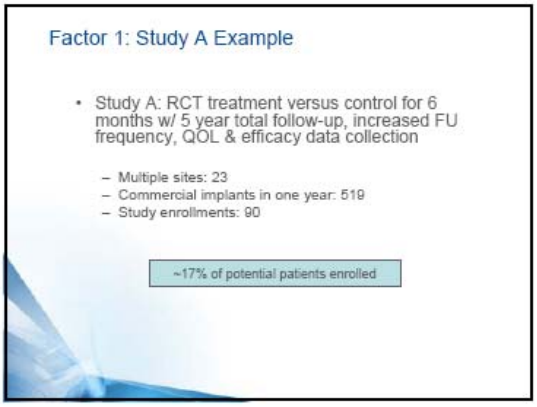
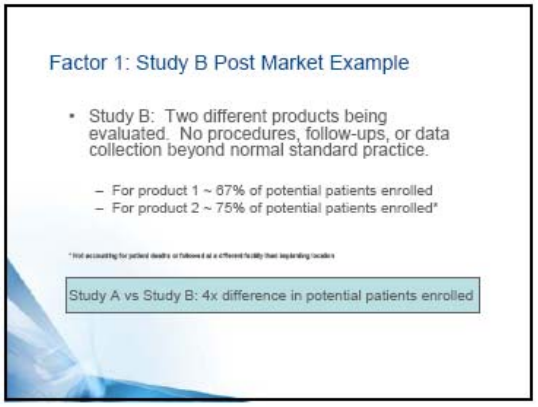
ATTACHMENT F: Presentations









Factor 2: PAS Regulatory Pathway

- PMA-S route increases time to make needed protocol modifications to address any recruitment issues
  - Example
    - PMA-S to modify protocol took 153 days for first FDA response to supplement (5x longer than pre-approval IDE review)
    - After response – another 103 days for response/approval (3x longer than IDE)

Total FDA time on supplement = 256 days

Factor 3: Reimbursement and IRBs

- Because of the size and duration of PAS studies sponsors seek reimbursement for standard of care costs
- Some confusion over PAS from payors and IRBs regarding "investigational" status
- Payment can occasionally become challenging encouraging patients and physicians to simply do a commercial implant
- Alternative is fully funding trial – however cost can be > than revenue for product

Recommendations

- OSB should continue to ensure alignment with pre-approval branch to clearly understand what is truly necessary from PAS
- Align PAS design with standard practice for that device with appropriate compliance oversight from sponsor (site selection, monitoring)
- Target 30 day review cycle for PAS approvals and subsequent supplements: parallel to IDE regulatory pathway for premarket studies
- Clear guidance from FDA to IRBs and others regarding "non-investigational" status of these approved products

Post-Approval Studies: Challenges and Opportunities

Danica Marinac-Dabic, MD, PhD
Director, Division of Epidemiology

Office of Surveillance and Biometrics
Center for Devices and Radiological Health
Food and Drug Administration

Fuel of Choice: Sunlight

PAS: Proper Study Design and Hypothesis

Anticipation

PAS: Detailed Scientifically Sounded Protocol

The Struggle

PAS: Implementing Study

On the Way

PAS: To Accomplish Post-Approval Commitments

Postmarket Context

- Reporting of Adverse Events & Product Problems
  - Medical Device Reporting
  - Medical Product Surveillance Network
- Post-Approval Studies
- Postmarket Surveillance
  - Section 522 of the Federal F, D & C Act
- CDRH Epidemiologic Research Program
- FDA Sentinel Initiative

Post-approval Studies (PAS)

- Required studies on highest risk devices (class III PMA devices)
- Ordered at time of approval with agreed upon protocol as goal
- Authority under CFR Title 21 Section 814.82
  (a) FDA may impose post-approval requirements at the time of approval of the PMA
  . . .
  (2) Continuing evaluation and reporting on the safety, effectiveness, and reliability of the device for its intended use. . .

PAS – Established Need

- Gather essential postmarket information
  - Longer-term performance including effects of re-treatments & product changes
  - Real-world device performance (patients and clinicians)
  - Effectiveness of training programs
  - Sub-group performance
  - Outcomes of concern (safety and effectiveness)
- Balance premarket burdens
- Account for Panel recommendations

Post- Approval Studies Vision

- Important postmarket questions are addressed
- Studies are founded on good science, are timely and provide useful results
- Existing external databases infrastructure is fully utilized/explored
- Stakeholders are kept apprised
- Collaboration is stressed throughout
- Enforcement options are rarely used

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Major Goals of PAS Program Transformation

- Enhance scientific rigor of PAS
- Establish and maintain accountability for PAS commitments
- Build PAS information management system
- Link postmarket knowledge to premarket device evaluation
- Increase transparency with the public

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PAS Oversight

January 1, 2005 Initial Transfer

April 2, 2007 Full Transfer

ODE/OIVD

OSB

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Premarket Review Process

- Postmarket Section recommended for each PMA
- Epidemiologist on each PMA team
  - Review premarket data
  - Help design the PAS
  - Work interactively with sponsors
  - Goal - PAS protocol finalized before or at the time the PMA approval

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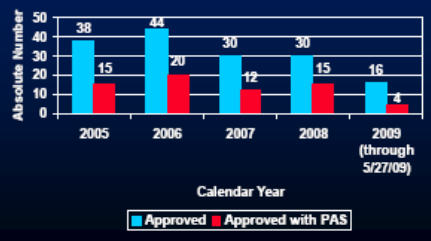
Number of Approved Original PMAs and Panel-Track Supplements



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Percent of Original PMAs and Panel-Track Supplements Approved with PAS Requirement(s)

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PAS Tracking System

- Developed & instituted automated tracking system for post-approval study commitments
- Ongoing 162 PAS (127 orders)

Postmarket Review Process

- Epidemiologist is the lead on all PAS Reports and all PAS Supplements involving changes to PAS protocol
- Postmarket Review Team
  - Feedback to premarket/CDRH networks

PAS Guidance Document

Guidance for Industry and FDA Staff:

Procedures for Handling Post-Approval Studies Imposed by PMA Order (December 21, 2006, revised August 1, 2007)

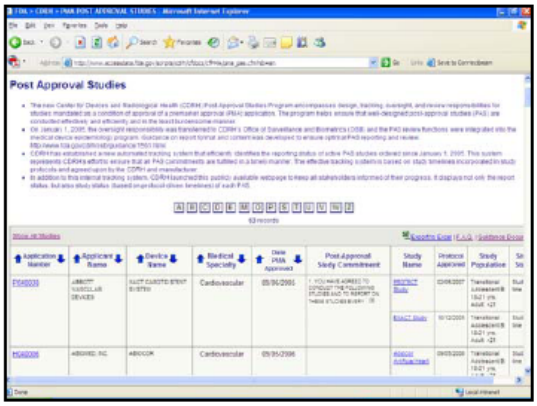
http://www.fda.gov/cdrh/osb/guidance/1561.html

PAS Web Page

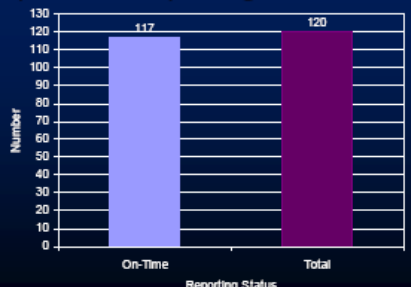
Went live on April 6, 2007

- Reporting Schedule Status
- PAS Study Progress
- Post – 2005 Studies

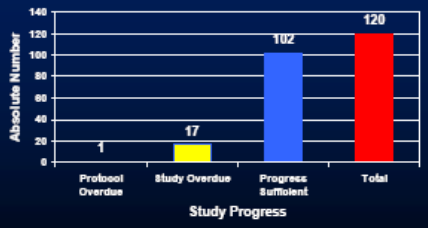
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma_pas.cfm



Sponsors Reporting Status: 2009



Study Progress for PAS Ordered 2005 to present



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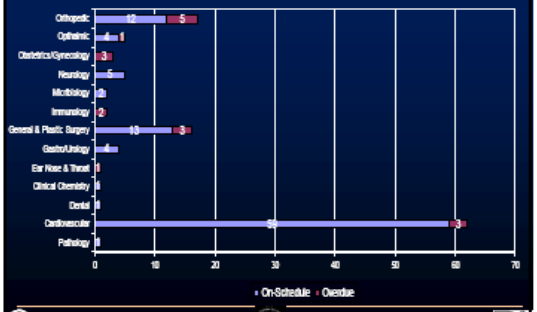
PAS Study Progress Status: 2009



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Opportunities

- Lead the development of postmarket infrastructure
- Advance postmarket science
- Augment existing postmarket tools
- Develop and apply innovative study methods to answer postmarket questions
- Be integrated into FDA Sentinel Initiative

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Questions, Comments, Ideas?

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Division of Epidemiology — Food and Drug Administration


RxTrials
Research Site Experts
Research Site Experts
The Site's Perspective
Investigative & Patient Recruitment
Post-Approval Studies for Medical Devices
FDA – June 4-5, 2009
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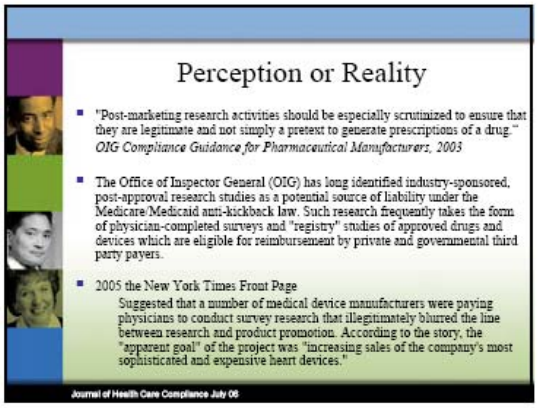
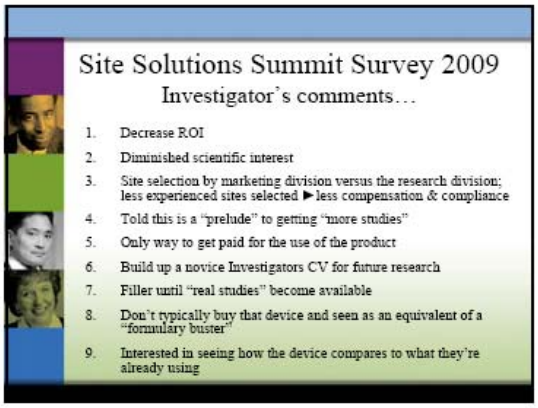
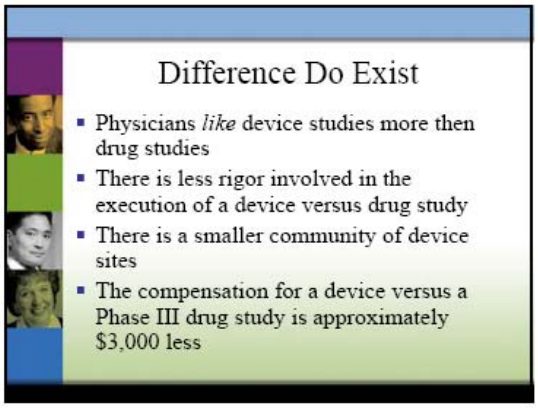
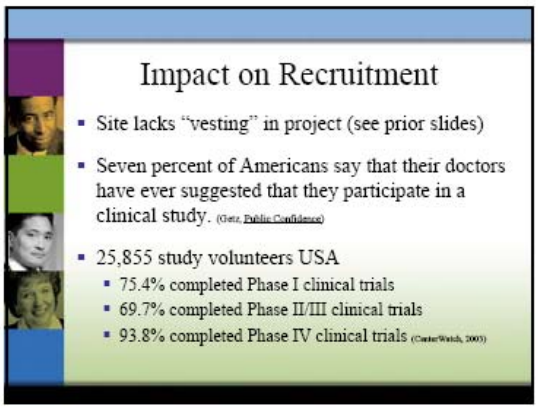

Perception or Reality
"Post-marketing research activities should be especially scrutinized to ensure that they are legitimate and not simply a pretext to generate prescriptions of a drug."
OIG Compliance Guidance for Pharmaceutical Manufacturers, 2003
The Office of Inspector General (OIG) has long identified industry-sponsored, post-approval research studies as a potential source of liability under the Medicare/Medicaid anti-kickback law. Such research frequently takes the form of physician-completed surveys and "registry" studies of approved drugs and devices which are eligible for reimbursement by private and governmental third party payers.
2005 the New York Times Front Page
Suggested that a number of medical device manufacturers were paying physicians to conduct survey research that illegitimately blurred the line between research and product promotion. According to the story, the "apparent goal" of the project was "increasing sales of the company's most sophisticated and expensive heart devices."
Journal of Health Care Compliance July 06


Site Solutions Summit Survey 2009
Investigator's comments…
1. Decrease ROI
2. Diminished scientific interest
3. Site selection by marketing division versus the research division; less experienced sites selected ►less compensation & compliance
4. Told this is a "prelude" to getting "more studies"
5. Only way to get paid for the use of the product
6. Build up a novice Investigators CV for future research
7. Filler until "real studies" become available
8. Don't typically buy that device and seen as an equivalent of a "formulary buster"
9. Interested in seeing how the device compares to what they're already using


Difference Do Exist
Physicians like device studies more then drug studies
There is less rigor involved in the execution of a device versus drug study
There is a smaller community of device sites
The compensation for a device versus a Phase III drug study is approximately $3,000 less


Impact on Recruitment
Site lacks "vesting" in project (see prior slides)
Seven percent of Americans say that their doctors have ever suggested that they participate in a clinical study. (Getz, Public Confidence)
25,855 study volunteers USA
75.4% completed Phase I clinical trials
69.7% completed Phase II/III clinical trials
93.8% completed Phase IV clinical trials (CenterWatch, 2003)


Informed Consent &
The Realities on Participation
Which would you prefer?

Drawn Together, But Not an Easy fit

- Regulatory consistency
- Industry consistency
- Utilization of Medicare to help gather AE information
- The volunteers, they'll come as we address the BIGGER picture related to clinical research, *but that's a different topic*

Thank You

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Implementation of Post-Approval Studies for Medical Devices

Challenges in Patient Recruitment and Retention
Industry perspective on patient retention

David R Rutledge, Pharm.D., FCCP, FAHA
Director, Worldwide Clinical Affairs

Abbott

Challenges in patient recruitment and retention

- Over the past 3 years, patient recruitment and retention have become:
  - Easier
  - The same
  - More frustrating
  - More expensive
  - More labor intense
  - More time consuming
  - More complex

Challenges in patient recruitment and retention

- Over the past 3 years, medical device companies are becoming more pharma like:
  - Strongly disagree, absolutely not, we are very different, and that's that!
  - Moderately disagree
  - Agree
  - Moderately agree
  - Strongly agree
  - I really don't know



Dispelling Myths About IDE vs. Post-Approval Trials

- Quantity of data
- Quality of data
- Quality of sites and sophistication of the staff
- Infrastructure needed (number of patients involved)
  - Trying to follow 2 to < 20 patients is different from the coordination needed to follow 20 to 200 patients from a particular site
- Monitoring (100% to 0%) [Guidance needed] Dirty secrete.
- Type of information collected or needed
  - Required versus "if available" according to standard of care
  - "If available" means "If it is there" not "If it is conveniently available"

Dispelling Myths About IDE vs. Post-Approval Trials (cont.)

"And this is where our ROI became an IOU."

Dispelling Myths About IDE vs. Post-Approval Trials (cont.)

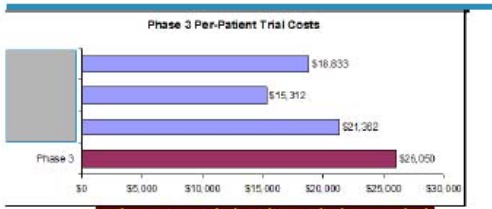
- Budget requirements
  - Reimbursement issues: "If this is research, companies should pay."
  - Fair Market Value: Greater scrutiny for trials involving commercial products

That's not fair!

FMV → Send to sites ↔ Start negotiating ↔ Competitors

  - Total costs vs. per patient costs
  - Pressures to outsource
  - Which team chronically says, "We need more resources!!"?

Phase 3 Per-Patient Trial Costs Comparison



Limited and more restricted set of investigators and patients
A core day-to-day activity for many sites
Usually pay for the investigational procedure and device
100% monitoring
Prestige associated with participation

Source of Data: Cutting Edge Information – Report: Clinical Operations: *Accelerating Trials, Allocating Resources & Measuring Performance*

Phase 4 Per-Patient Trial Costs Comparison

Broader and more diverse set of investigators and patients
A supplement to day-to-day patient care activities
Usually don't pay for the procedure or the device
Huge variability in monitoring
Greater pressures to outsource and to use OUS/XUS sites
The promise of prestige to come

Source of Data: Cutting Edge Information – Report: Clinical Operations: *Accelerating Trials, Allocating Resources & Measuring Performance*

Patient Retention: Protocol
Internal Financial Pressures

Patient Retention: Protocol

- Extend eCRF windows for data entry and analysis, e.g., 5 day or 45 day parameter
- Obtain five other **contact** phone numbers: extended family, primary care physician, cell phones, email addresses, micro chips?, etc.
  - Support multiple attempts such as call at least 5 times, send certified mail, work with referral or primary physician
- If it's in the protocol, it needs to be in the **informed consent**
  - You are consenting them for future follow-up so patients are not caught off guard
  - Specify in the Inclusion/Exclusion criteria that the patient be willing and able to undergo all follow-up visits

Patient Retention: Protocol (cont.)

- Avoid **protocol deviations** so look for specific ways to decrease them
  - "If available"
  - Standard of care
- Set the tone at **investigator** meetings, especially in coordinator breakout sessions
  - Have a panel to discuss tips for success and address potential issues/challenges from the past (Share best practices)
  - How will you deal with investigator "no shows" or those that leave early?
- Ensure patients are aware of **compensation** for travel costs which could be included in the protocol, flyer for recruitment, informed consent, patient brochure, web site, etc.
- Create a study brand and message: "Get connected"
  - Patients have a desire to meet other participants

Patient Retention: Protocol
Internal Commercial Pressures

You started designing clinical trials? I thought you were in Marketing?

Patient Retention: Patient-related factors

- Ask patients what motivates them to return and then build programs around that
  - What's in it for me, the patient?
- Address patient information needs (increasing order of importance)
  - Information about my illness
  - General clinical study information
  - Glossary of terms
  - What to expect at each visit and flexible hours at the site
  - Directions and logistics (area map to where they sign in). Access to public transportation.
  - FAQs
  - Access to their results
- Referring subjects to the hospitals or clinics that are more convenient for them is another way as long as there is no complex test needed at follow-up
- Use phone calls as much as possible and at times they choose
- Some patients want free medical check-ups for family members during their follow-up visits
- Let subjects know that they have access to a 24 hour nurse (usually) at site

Patient Retention: Patient-related factors (cont.)

- Stress that there is better patient care than outside of a trial (more visits, more calls)
  - Offer unprecedented care!
- Participants want to talk with a specialist or provider on an ongoing bases during the course of the trial
- "You have opportunities to prevent an event" (problems with refills of clopidogrel?)
- Sponsor may initiate a patient assistance program
  - Identify and address specific reimbursement issues
- Inform participants of study results as they become available
- Develop online patient portals that they can access
  - Survey them to identify issues that need to be addressed to encourage them to remain in the trial
- Paying for logistic and transportation costs
- Add that their compliance is an altruistic gesture for others later on
  - "What you are doing may help others." Demonstrate the value of their contribution.

Site Selection: Location, Location, Location

Site Issues: Site selection and assessment of local support

- Avoid sites with limited clinical experience/research staff
- PI doesn't mean "Partially Involved" or "Practically Invisible"
  - Review PI, Co-I, and Research Coordinator CVs thoroughly
  - There is a difference between "**collecting**" versus "**assessing**" them
- Slowly weed out non-performing sites and manage consequences
  - Put them on a performance improvement plan (**PIP**), like we do non-performing employees. May affect future relationships
  - Burdensome protocols, consenting patients, accurate case report forms, and adhering to timelines are tasks conducted by **study coordinators**
  - Simply increasing Investigator study **grants** for ailing studies is not the answer when study workload is carried by study coordinators

Site Issues: Site selection and assessment of local support

- Sites typically will have different needs
  - Don't make assumptions as to what they understand (GCP, etc.)
  - eCRF training (when to enter data, time windows)
  - Prefer low burdensome protocols
  - Help with regulatory-related processes (informed consent, safety, audits)
  - Preparing for an on-site visit (what will happen, staff available, documents)
  - Help with study start up, ongoing support, and close out
    - **Data cleaning requirements, final queries, and archiving requirements**
  - Some will start fast and finish slow, start fast and not finish, start fast and finish fast, start slow and finish fast, etc.
  - "Is it okay to enroll all my patients in year two?"
  - Address no double dipping with payers
  - Promote the value of participating: provide pt. reports that they can use

Site Issues: Site selection and assessment of local support

- Situation
  - "The legal guys say we need these 10 page informed consents because that's what our SOP says."

What was behind this?

Post-approval trial is not a pivotal (experimental) trial
Same can be said about site contracts
Change/update your SOPs

Site Issues: Site selection and assessment of local support (cont.)

- Consider a performance based program that rewards coordinators for achieving study objectives, quality of data, patient care, and responsiveness to queries
  - Develop quantifiable incentive/metric programs
- People at sites move, so communicate often
  - loss of PI and coordinator leadership can increase costs
- Ask sites to provide metrics on long-term follow-up success rates
- What tools do they have for recruitment and retention? Languages needed?
- What systems are in place when you have to go into the "rescue" mode?

Site Issues: Site selection and assessment of local support (cont.)

- Address trial competition for patients at sites
- Assess the number of additional trials a site is participating in
- Compare sites as to whether other companies are using them too
  - Careful if they are not
  - Could be either a "red flag" or "diamond in the ruff"
- Assess how they identify patients for studies, e.g., electronic patient data entry that connects patient factors with studies
  - Cleveland Clinic, MAYO
- Use American Heart Association "Get With The Guidelines" Hospital List April 2009
  - Coronary Artery Disease, Heart Failure, Stroke: tells you systems are in place
  - www.americanheart.org/presenter.jhtml?identifier=3057983

Performance Achievement

GWTG

www.americanheart.org/presenter.jhtml?identifier=3057983

Performance Awards

These awards recognize hospitals that demonstrate at least 85 percent compliance in each of the six GWTG-CAD Achievement Measures.

Levels reflect the amount of time for which the hospital demonstrates performance.

Bronze recognizes performance of 90 consecutive days.

Silver recognizes performance of 12 consecutive months.

Gold recognizes performance of 24 consecutive months or more.

Achievement Measures for GWTG-CAD are embedded in the Patient Management Tool:

- Early Aspirin
- Aspirin on Discharge
- Beta Blocker on Discharge
- ACE/ARB in CAD patients with LVSD
- Lipid Management (2)
- Smoking Cessation

Prevention
ATP III
JNC VII

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Performance Achievement

GWTG

www.americanheart.org/presenter.jhtml?identifier=3057983

The American Heart Association and American Stroke Association recognize the hospitals listed below for their success in using Get With The Guidelines to improve quality of care for heart disease and stroke patients.

Hospitals that have earned a **Gold Performance Award** follow treatment guidelines in certain key measures at least 85 percent of the time, and have maintained this performance level for two years or more. **Silver Performance Award** hospitals have maintained this performance level for one year.

Hospital Name	City	Gold	Silver
Delaware			
Bayhealth Medical Center - Kent General	Dover	HF	
Bayhealth Medical Center - Milford Memorial	Milford	HF	
Christiana Care Health System	Newark	CAD	
District of Columbia			
Georgetown University Hospital	Washington		S
Florida			
Aventura Hospital and Medical Center	Aventura		S
Baptist Medical Center	Jacksonville		S
Bay Pines VA Healthcare System	Bay Pines		S
Bayfront Medical Center	St. Petersburg	S	
Bethesda Memorial Hospital	Boynton Beach		S
Blake Medical Center	Bradenton	S	
Broward General Medical Center	Ft. Lauderdale		S
Cleveland Clinic Florida	Weston	CAD S HF	

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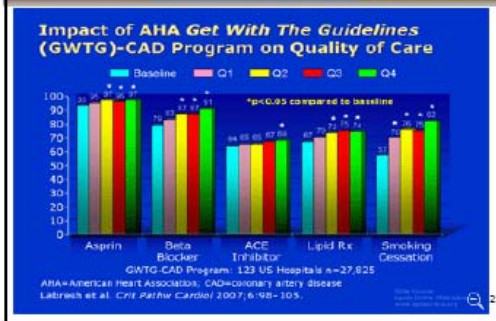
Performance Achievement

GWTG



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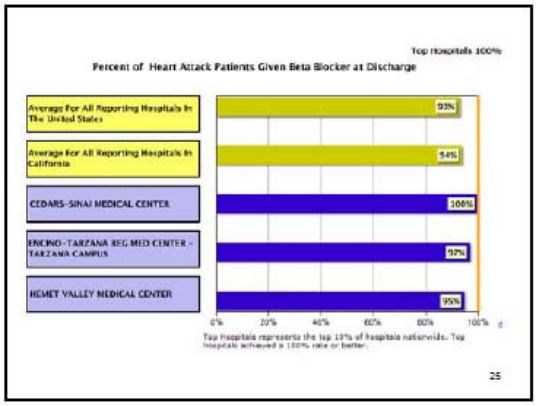
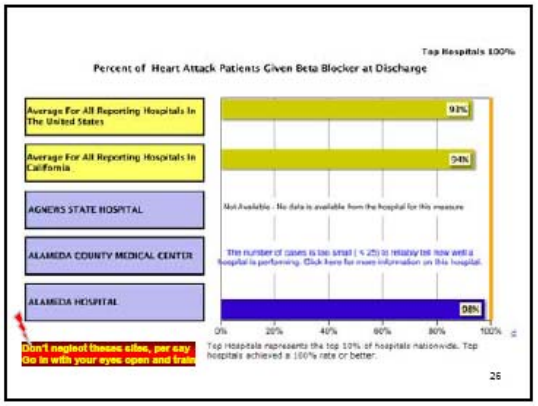
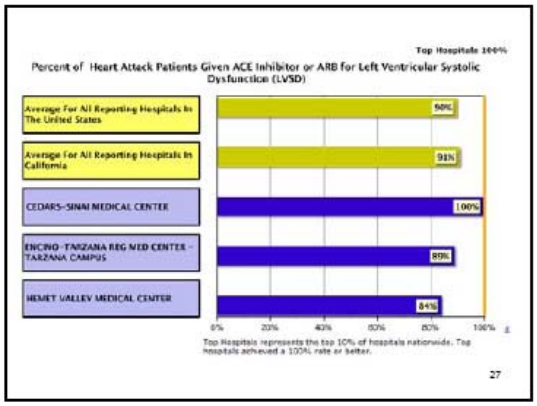
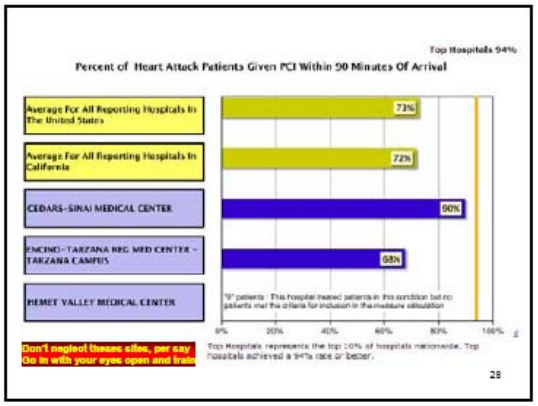
Site Issues: Site selection and assessment of local support (cont.)

- Use U.S. Dept of Health and Human Services: **Hospital Compare**
  - a quality tool provided by Medicare
  - www.hospitalcare.hhs.gov/hospital/









Site Issues: Working with sites that are selected

- **Clinical coordinators are key, but they come and go and work on multiple studies**
  - The studies that pay more get more attention
  - Set expectations at the first visit
  - Provide tools for coordinators to screen, consent, enroll, and follow patients
  - Flow charts, scripts, calendars, post-cards, worksheets
  - Communicating back could help retain patients in your study
- **Consider forming a Clinical Coordinators' network**
  - Support monthly teleconferences during enrollment, then quarterly as study progresses to the follow-up phase
  - Regionalize these so that there are no (or fewer) time zone issues
- **Have each site deliver a recruitment and retention plan**
- **How will you inform your referral groups?**
- **PIs and Co-Is (set expectations)**
  - Regular teleconferences
  - Value proposition (grants are lower so WIIFM?) (data, presentations/publications, ISS)

Better science but at a price

Sponsor = label extensions, changing guidelines, performance goals

Site Issues: Working with sites that are selected (cont.)

- When talking with patients, have sites ask what else they are interested in discussing with health care provider on their return visit
- Involve family members too if okay with the patient
- Pay patient stipend at the end of their visit
- From a behavioral perspective, elderly patients state the stability of staff as important
- Have sites identify logistical issues
  - There are competing agendas
    - Pressures on enrollment needs to balance with pressures for follow-up
  - Confirm patient visits in advance
    - Communication with patients prior to the window they need to show up so they can plan to come in ahead of time (phone, email, etc.)
    - Communicate regularly with your patients using newsletters, phone calls, internet web sites, postcards, etc.
    - Avoid waiting to right when they need to come in

Sponsors have caused this!

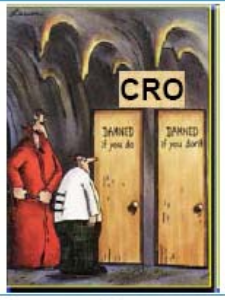
Site Issues: Working with sites that are selected (cont.)

- Request metrics on customer satisfaction with clinical trial staff
- Ask if there would be value in recruitment and retention training by the Sponsor
- Communicate site recruitment and retention rates among sites
- Continue to remind sites what your expectations are

Site Issues: Site selection and assessment of local support (cont.)

- Budgets
  - Stress completion of patient visit eCRF for sponsor compensation
  - Most sponsors include a standard advertising budget for each study site
    - Few sponsors make sites accountable for tracking advertisement responses and then reporting metrics
    - Assist in media buying expertise in order to place cost-effective advertising
  - Ask sites, "Do you believe the recruitment and retention budget is adequate for you to achieve our goal?"

Working with CROs



Working with CROs

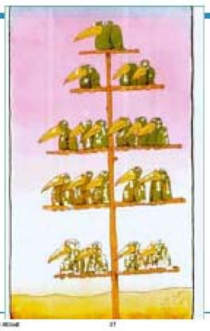
- Choose those with experience in Post-Approval studies
  - Sometimes dictated by Preferred Vendor status with the Sponsor
- Communicate, communicate, communicate
- Set realistic enrollment and retention goals
  - Empower CROs to achieve retention goals
  - Have specific and clearly stated expectations in contracts
  - Don't underestimate the amount of data cleaning before data lock and generation of statistical tables
- Performance-based incentives work (carrot not the stick)
- Exploit novel, time efficient remote monitoring plans
- Address your expectations early in terms of number of site contacts and how often between contacts when communicating with sites
  - phone, email, certified letters, site visits

Working with CROs (cont.)

- Regulations are silent on transfer of regulatory obligation
  - Can't abdicate responsibility
  - CROs (and Core Labs) are not covered in device regulations
    - 21 CFR 312. vs. 21 CFR 812
- Identify when you start contingency planning
- Conduct a lessons learned analysis

Harmonization Desired

Senior Management Support



Senior Management Support

- **Misunderstandings about quality in Post-Approval studies**
- **People lost to follow-up are usually feeling better**
  - Yes you will pick up deaths, but you will get those that feel well which increases the denominator and generates better data
- **Estimate the value of 10 (or 100) patients**
  - Look at retention like an insurance policy. Initiating a retention program early on protects a Sponsors' investment and the statistical power of the data
  - Every time a patient drops from the study the value of the remaining participants increase
  - Sample size is directly linked to (positive) outcome measures
  - There is a risk that your outcome measure will suffer if you lose patients
  - Loss of statistical power? Now you really have a problem.
- **Show how you might use this data for performance goal setting to decrease future costs of other clinical studies**
- **Show how you might use this data for potential label extensions for a competitive edge**
- **Communicate that slow enrollment increases cost of follow-up**

Benefits vs. Risks: Post-Approval

Benefits to Franchise \ Risks to Franchise	Low	Moderate	High
High	++++	+++	+/--
Moderate	+++	++/--	---
Low	++/-	---	----

What company factors influence this?

Benefits vs. Risks: Post-approval

Benefits to Franchise \ Risks to Franchise	Low	Moderate	High
High	++++	+++	+/--
Moderate	+++	++/--	---
Low	++/-	---	----

Product life-cycle
Market size & share

Leadership Philosophy
Regulatory Guidance

Previous warning letters
Corporate Integrity Agreement

8 Post-approval take away messages

1. Patient recruitment and retention is becoming more **labor intense, time consuming**, and **complex**
2. **Quality** is still a relevant word when speaking of protocols, data collection, and site selection
3. Issues remain regarding appropriate **budgets** in terms of reimbursement challenges, FMV, monitoring, and outsourcing
4. Assess and then address **patient-related factors**
5. Don't underestimate the value of focusing on clinical **coordinators**
6. **Empower** CROs to achieve your goals
7. Address Sr Management's **misunderstandings**
8. Working **together** in forums like this will help all of us!

Things I have learned

10 things I have learned working in a regulated pharmaceutical or device industry

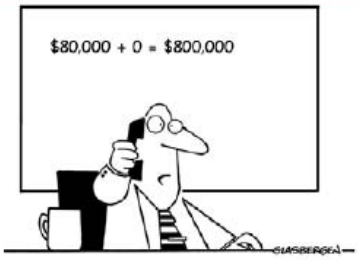
Sr Leadership Communication

"I'd like your honest, unbiased, possibly career- ending opinion."

Team Success

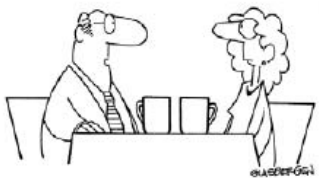
"Don't forget, I need to be taking credit for that report by three."

Budgets need to be justified and transparent!



What may be obvious to some may not be for others

Resource Issues



"These days I'm semi-retired. I'm only working 40 hours a week."

Don't lose site of the main thing!

Do more with less!

"I liked the motivational ones better."

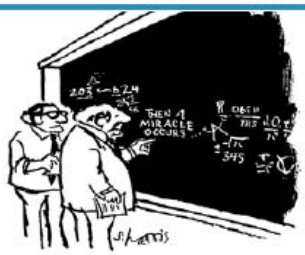
The Spin

"Would you please elaborate on 'then something bad happened'?"

There are plenty of suggestions

"Yes, I received your suggestion. Let me fly it by some people and see what kind of reaction it gets."

Discussions with Regulatory Agencies



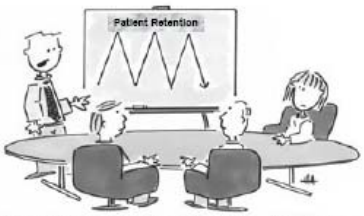
"I think you should be more explicit here in step two."

Questions?

- David R Rutledge, Pharm.D., FCCP, FAHA
  Director, Worldwide Clinical Affairs
  david.rutledge@av.abbott.com
  (408) 845-3820 Office phone
  (630) 846-0350 US Cell phone

"Hey, no problem!"

Patient Retention



"...and then another drop this month. But, I have a really good feeling about next month."

IMPLEMENTATION OF POST-APPROVAL STUDIES FOR MEDICAL DEVICES

CRO Perspective on Patient Retention

June 4, 2009

Clinical Trials Area

Nancy L. Dianis, RN, MS
WESTAT
Vice President and Associate Director

Westat Corporate Overview

- Incorporated 1963
- Headquartered in Rockville, Maryland
- International offices
- 100% employee-owned
- Clinical Trial Services—385+ employees
- Areas of Expertise
  - Health Statistics Surveys
  - Epidemiologic Studies
  - Phase 1 – 4 Clinical Trials

Pre-Market Studies and Post Market Studies Differences

- Purpose
- Duration
- Enrollment
- Retention

Attrition

- Reduction in numbers usually as a result of resignation, retirement, or death

Causes of Attrition

- Geography
- Inability to contact participant
- Refusal to continue

Guiding Principles for Participant Retention in Post Approval Studies

- Reduce barriers
- Inspire
  - What's in it for me (WIFM)
- Dynamic follow-up

Reduce Barriers to Participation

- Study site
  - Location
  - Hours of operation
- Technology
- Transportation
- Dependent care
- Expense

Inspire Participation

- Study population
  - Gender
  - Age
  - Culture
  - Device/Disease

Active Follow-Up System

- First response increases likelihood of retention
- Current accurate contact information
- Involve site PIs
- Sustain participant engagement
- Utilize tracing systems

Questions

Nancy L. Dianis, RN, MS
301-294-2885
Nancydianis@westat.com

IRB Considerations in Implementing Post-Approval Studies

Paul W. Goebel, Jr., CIP
President
Paul W Goebel Consulting, Inc.

pwgconsult@comcast.net
240 308 0601

FDA June 4, 2009

Protocol

- The protocol should state
  - the purpose of the study

IRB review

- The IRB must rely on the written documents and conversations with the sponsor or the investigator
- The purpose of the protocol not always succinctly stated in the study submission to the IRB

FDA Web site

- Buried 3-deep in CDRH
- Does not come up when post-approval studies is googled
- Web site outlines:
  - what must be submitted to FDA
  - The duties of the FDA reviewers
- IRBs not mentioned in guidance
  - Information required to be given to IRBs not outlined

IRB uncertainties

- Are Post-approval studies Significant Risk?
- FDA requirement not stated

SR/NSR

- **Significant Risk (SR) needs IDE filed with, and approved by, FDA**
- **Non-significant Risk (NSR) no FDA notification or approval needed, only IRB approval**
- **IRB makes final SR/NSR call when sponsor claims study is NSR**

Apparent Double Standard

- IRB seen as a partner to FDA when reviewing NSR studies
- But only given access to publically available study information

- FDA needs to rethink policy of denying IRBs access to all proprietary study information.
  - Not really confidential any more
  - All competitors already know
  - Get needed information to IRBs with minimal effort

Patient Recruitment & Retention:

Where are we now?

Where are we going?

Presented June 4, 2009 at FDA's CDRH workshop

Diane Simmons, President and CEO
Center for Information and Study on Clinical Research Participation

Public Confidence & Trust Today

General Public Attitudes:
70%-83% of Americans believe clinical research is 'very important' or 'essential' to advancing public health

Perception of Clinical Research Professionals:
42% of Americans distrust biopharmaceutical companies; only 14% believe they are 'honest' to public (similar rating for tobacco, oil & used car sales industry)

31% of Americans believe the FDA is effective at ensuring public/patient safety

25% of Americans believe that PIs and study staff are solely motivated by greed

4 Distinct Patient Communities

THE PUBLIC PRE-PARTICIPANT	PROSPECTIVE PARTICIPANT	STUDY PARTICIPANT	PAST PARTICIPANT
No Context, No Connection	Forced to Self Advocate	Part of the Study Team	Excused from the Study Team
High exposure and recall of recruitment ads and breakthrough announcements	Higher exposure and recall of recruitment ads and breakthrough announcements	Give HIGH marks for level of professionalism, quality of care and attentiveness	High willingness to participate in another clinical trial
	High interest in participating; low awareness of HOW	Informed Consent generates HIGH comprehension of trial logistics but NOT RISKS	No follow-up; no sense of connection or assurance of contribution or VALUE

Lessons Learned & Impact

- Public trust is getting in the way of people recognizing and enrolling in clinical trials.
- Public education and outreach impact not only long term awareness and support but also short term recruitment and enrollment rates.
- A variety of organizations – patient advocacy groups, investigative sites, government agencies, sponsors and CRO companies - are implementing a public service campaign and other public education and outreach initiatives.

'Medical Hero' Public Service Campaign

- Not study specific
- Addresses broader benefits of clinical research
- Has a call to action for further information
- Multimedia approach
- Collectively embraced by stakeholders in clinical research and healthcare
- Longevity

Complementing trial-specific recruitment messages

- Where they are already buying print, radio or TV media, they are exchanging 5% to 10% of their recruitment ads with the 'Medical Heroes' message.
- Using the 'Medical Heroes' print ads as posters and fliers in the waiting rooms of doctors offices, hospitals, and community health clinics, and these are placed along side their trial recruitment posters and fliers.
- Playing 'Medical Heroes' radio and TV ads on DVD players in waiting rooms and offices.
- Providing visible links online to 'Medical Heroes' campaign.

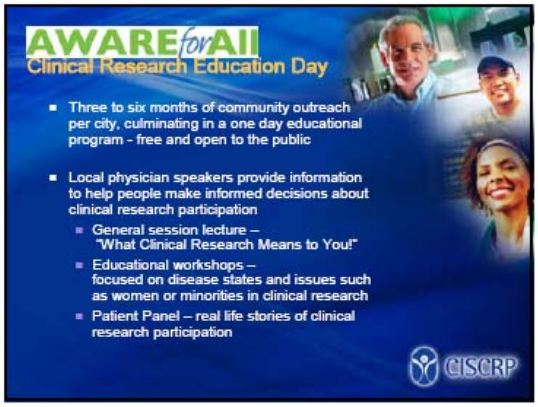

Lessons Learned & Impact
Market test by sponsor: Ran the 'Medical Heroes' campaign concurrent with recruitment ads for a pain study in 30 sites across 18 different US locations.
Market test result: 38% increase in recruitment rates.
Observing significant increase (35 – 45%) in inquiries by phone and on website with CISCRP providing responses to questions and free educational brochures as follow-up.
Greater visibility – reach and frequency – improves awareness.
CISCRP


Limited Impact without effective public education
74% say they have no 'real' knowledge of the clinical research process
98% don't know where and how to identify and evaluate appropriate clinical studies
Source: CenterWatch; CISCRP; Harris Interactive
CISCRP

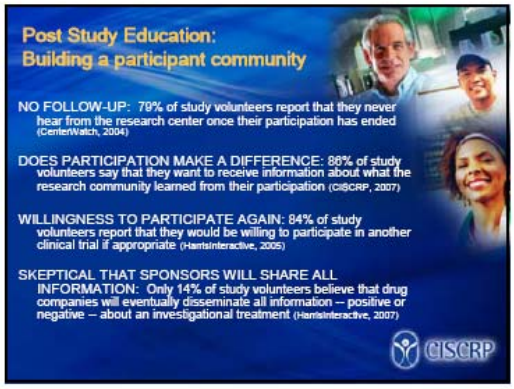

From whom does the public learn about clinical trials today?
Less than 17% of volunteers report that they learned about clinical trials from their primary/specialty care physician (TCSDD, 2007)
Greater disparities among minority patients
Less than half of physicians refer patients into clinical trials with a typical referral rate of <1% of community served (TCSDD, 2007)
CISCRP

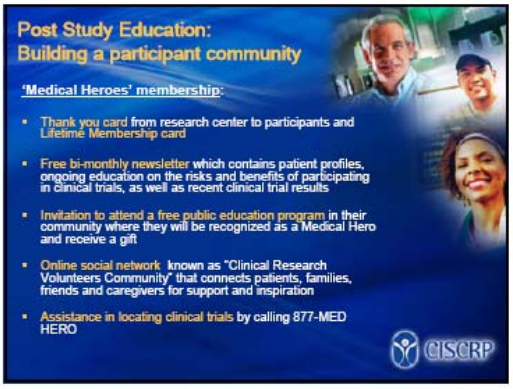

Growing use of social networks and online listings/registries
Commercial social networking sites (e.g., Facebook)
Social networking & registries through patient advocacy groups
'Clinical Research Volunteers Community' on www.medhero.org
Search Clinical Trials - new consultative service of helping the public find trials that are listed on public registries
CISCRP

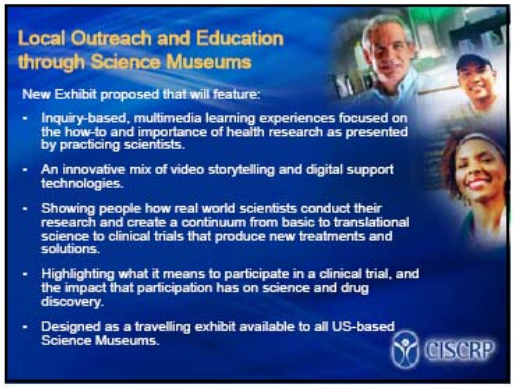

Intensifying efforts with Grassroots programs…
Take awareness-building into the heart of the community utilizing traditional outreach and advocacy strategies
Put a face on the research and health provider communities
Build a movement at the local level by engaging and informing political figures, opinion leaders, physicians, healthcare providers, and community organizations
CISCRP

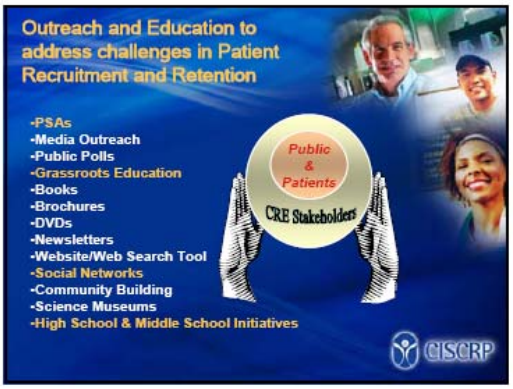

AWARE for All
Clinical Research Education Day
Three to six months of community outreach per city, culminating in a one day educational program - free and open to the public
Local physician speakers provide information to help people make informed decisions about clinical research participation
General session lecture – "What Clinical Research Means to You!"
Educational workshops – focused on disease states and issues such as women or minorities in clinical research
Patient Panel – real life stories of clinical research participation
CISCRP


Community Building model
(prospective interest from
Clinical and Translational Science Institutes)
PAYORS
POLITICIANS & POLICY MAKERS
DISEASE SPECIFIC GROUPS
OPINION LEADERS
working together to help people make informed decisions about clinical research participation
RESEARCH CENTERS
COMMUNITY HEALTH CENTERS
ACADEMIC MEDICAL CENTERS
FAITH BASED GROUPS
CISCRP


Post Study Education:
Building a participant community
NO FOLLOW-UP: 79% of study volunteers report that they never hear from the research center once their participation has ended (CenterWatch, 2004)
DOES PARTICIPATION MAKE A DIFFERENCE: 86% of study volunteers say that they want to receive information about what the research community learned from their participation (CISCRP, 2007)
WILLINGNESS TO PARTICIPATE AGAIN: 84% of study volunteers report that they would be willing to participate in another clinical trial if appropriate (HarrisInteractive, 2005)
SKEPTICAL THAT SPONSORS WILL SHARE ALL INFORMATION: Only 14% of study volunteers believe that drug companies will eventually disseminate all information -- positive or negative -- about an investigational treatment (HarrisInteractive, 2007)
CISCRP


Post Study Education:
Building a participant community
'Medical Heroes' membership:
Thank you card from research center to participants and Lifetime Membership card
Free bi-monthly newsletter which contains patient profiles, ongoing education on the risks and benefits of participating in clinical trials, as well as recent clinical trial results
Invitation to attend a free public education program in their community where they will be recognized as a Medical Hero and receive a gift
Online social network known as "Clinical Research Volunteers Community" that connects patients, families, friends and caregivers for support and inspiration
Assistance in locating clinical trials by calling 877-MED HERO
CISCRP

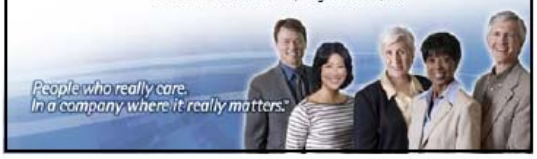

Local Outreach and Education through Science Museums
New Exhibit proposed that will feature:
Inquiry-based, multimedia learning experiences focused on the how-to and importance of health research as presented by practicing scientists.
An innovative mix of video storytelling and digital support technologies.
Showing people how real world scientists conduct their research and create a continuum from basic to translational science to clinical trials that produce new treatments and solutions.
Highlighting what it means to participate in a clinical trial, and the impact that participation has on science and drug discovery.
Designed as a travelling exhibit available to all US-based Science Museums.
CISCRP


Outreach and Education to address challenges in Patient Recruitment and Retention
-PSAs
-Media Outreach
-Public Polls
-Grassroots Education
-Books
-Brochures
-DVDs
-Newsletters
-Website/Web Search Tool
-Social Networks
-Community Building
-Science Museums
-High School & Middle School Initiatives
Public & Patients
CRE Stakeholders
CISCRP

Omnicare Clinical Research

Recruitment of Clinical Sites for Post-Approval Studies for Medical Devices

Steven Pashko, PhD
Sr. Vice President, Global Late Phase Studies, Pharmacovigilance and Safety
Omnicare Clinical Research, King of Prussia, PA



Operational Definition

Site Recruitment

- Site identification through study initiation
  - Through completion of all regulatory documents required prior to first patient enrollment

General Site Requirements

- Adequate and qualified clinical research staff available for the duration of the study
- Adequate procedures, facilities and equipment
- Ability to recruit a specified number of subjects within the recruitment timeline
  - Lack of competing studies that might thwart enrollment
- Ability to complete required documentation within a reasonable time frame

Specific Site Requirements

- Experience with indication (previous studies)
- Quality (FDA 483, MHRA findings)
- Ability to identify and enroll appropriate patients
- Ethics committee (local/central, frequency)
- Study agreement (timeline/ costs)
- Privacy assurance (HIPAA compliance)
- Medical record format (electronic/ paper)
  - Use of electronic data capture

Sources Used to Identify Phase IV Device Sites

- Medical directories/ associations, research literature, etc
- Academic medical center hospitals
- Commercial databases
- A sponsor listing of investigators
- CRO investigator recruitment database

Large, simple, post-approval trials will utilize large datasets (e.g., medical association)

Device studies may require more use of hospitals

Large Trial Device Issues

- Time horizons may be long
  - Investigator drop-outs increase over time
- No historical standard by which one can estimate enrollment
  - What's too slow?
- Investigator sites are numerous
  - Culling databases is tedious and difficult
- Investigator payments are low
  - Little work-effort typically means little pay
- Patient payments are low
  - Few, simple visits are not burdensome
- IRBs may not have understanding of unusual studies
  - Use of "blanket approval"

Common Failure Points and Solutions

- Study Infeasibility
  - Acknowledge the power imbalances between sites, sponsors, and operations groups
    - Sites rarely say they cannot do a study
    - Sponsors seldom believe a study is infeasible
    - Operations groups want to do all studies
  - Conduct feasibility and offer results acknowledging these views
  - Study death by slow enrollment is often most preferable to this trio than no study at all
    - Yet it wastes everyone's time and money so it's best to prevent this from occurring

Common Failure Points and Solutions

- Lack of timely start-up
  - Contract haggling about finances
    - Uniform pricing
  - Contract haggling about legal wording
    - Uniform template
  - Ethics committee – non-administrative delays
    - Provide white papers supporting unusual key elements
      - Simplicity and use of blanket approval
      - Patient incentives

Thank You

HOGAN & HARTSON

Medical Devices: Post-Approval Studies

John J. Smith, M.D., J.D.

Post-Approval Studies: Legal Authority

HOGAN & HARTSON

Post-Approval Studies

- Clinical study or other investigation required in an approval order to gather specific information to address precise study objectives
- Imposed by order under the authority of Section 513(a)(3)(C) of the Federal Food, Drug, and Cosmetic Act (FDC Act) (21 U.S.C. § 360c(a)(3)(C))
  - Added by the Food and Drug Administration Modernization Act (FDAMA), and the post-approval requirements regulations at 21 C.F.R. § 814.82(a)

Post-Approval Studies: Legal Authority

HOGAN & HARTSON

21 U.S.C. § 360c(a)(3)(C)

- "In making a determination of a reasonable assurance of the effectiveness of a device for which an application under section 360(e) of this title has been submitted, the Secretary shall consider whether the extent of data that otherwise would be required for approval of the application with respect to effectiveness can be reduced through reliance on postmarket controls."

Post-Approval Studies: Legal Authority

HOGAN & HARTSON

21 C.F.R. § 814.82

- FDA may impose post-approval requirements at the time of approval of the PMA or by regulation subsequent to approval and may include:
  - (2) Continuing evaluation and reporting on the safety, effectiveness, and reliability of the device for its intended use. FDA will state the reason and the number of patients to be evaluated.
  - (9) Other requirements as FDA determines necessary to provide (continued) reasonable assurance of the safety and effectiveness of the device.

Post-Approval Studies: General Principles

HOGAN & HARTSON

- Objective: to evaluate device performance and potential device-related problems in a broader population over an extended period of time after premarket establishment of reasonable device safety and effectiveness.
- Post-approval studies (PAS) should not be used to evaluate unresolved issues from the premarket phase that are important to the initial establishment of device safety and effectiveness.

Post-Approval Studies: Program Transformation

HOGAN & HARTSON

- Oversight transitioned from Office of Device Evaluation (ODE)/Office of In Vitro Diagnostic Device Evaluation and Safety (OIVD) to Office of Surveillance and Biometrics (OSB) in January 2005 completed in April 2007
  - To ensure that adequate resources are devoted to the PAS program
  - January 1, 2005 — Initial Transfer
  - April 2, 2007 — Full Transfer

ODE/OIVD

OSB

Post-Approval Studies: Process

- Companies are generally required to include a PAS plan in a PMA submission unless CDRH concludes that a PAS is not necessary (less and less common)
- OSB staff epidemiologists are integral members of each PMA team
  - Lead the design of PAS study
  - Work interactively with sponsors
  - Present at Panel meetings
- PAS plan is presented at Advisory Panel meetings to solicit panel feedback
- PAS protocol/outline finalized at the time of PMA approval
- Agreed upon study timelines
- A PAS study should not mimic the pre-approval study
  - Designed to answer specific, unresolved questions from a pivotal study

Post-Approval Studies: Process

- CDRH and sponsor agree on protocol for post-approval study
  - If no agreement can be reached prior to PMA approval, sponsor should submit the study protocol as a PMA supplement within 30 days of PMA approval.
  - FDA is expected to act on and respond to the protocol submission within 60 calendar days of receipt.
  - If an agreement on a protocol cannot be reached, FDA may use its authority to order postmarket surveillance under section 522 of the act (21 U.S.C. § 360l; 21 C.F.R. Part 822).

Post-Approval Studies: Process

- Post-Approval Study Commitment
  - Agreement by the sponsor, confirmed by FDA in writing, to conduct one or more post-approval studies, completion of which will fulfill the post-approval study commitment
  - CDRH has been heavily criticized in the past for not enforcing agreed upon commitments
- Study Status Reports
  - Interim Post-Approval Study Status Report
    - Every 6 months for the first 2 years; annually thereafter
    - Written report to CDRH on the status of the PAS prior to completion
    - Status reports help assure that sponsors live up to their commitments
  - Final Post-Approval Study Report
    - Within 3 months of study completion
    - Written report based on terminated PAS or final results of agreed upon and completed PAS

Post Approval Studies: Compliance

- Possible results of failure to comply with post approval study requirements:
  - Post market surveillance under § 522 (21 C.F.R. Part 822)
  - Withdraw approval of PMA under § 515(e) (21 C.F.R. 814.46(a))
  - Civil money penalties
    - A significant or knowing failure to report information about a post-approval study; or
    - Such failure constitutes a risk to public health.

Summing Up

- Post-Approval Studies provide FDA with the tools to evaluate a new device over extended periods in broader populations
- Not a substitute for pre-approval data
- Evolving paradigm for FDA and industry

Drugs and Devices: Common considerations in Implementing Post-Approval Studies

Implementation of Post-Approval Studies for Medical Devices
June 4-5, 2009

Solomon Iyasu MD, MPH
Director
Division of Epidemiology
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
US Food and Drug Administration

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Disclaimer

- No conflicts to declare
- The view expressed here are mine and not necessarily of the FDA

2

Pre-approval Development

- Drugs
  - Usually Two Positive RCTs
  - Preclinical and Phase I-IV trails
  - A few hundred to a few thousands subjects
  - A few weeks to a year
  - No conditional approval
- PMA
  - Specific data required dependent upon device
    - Includes levels of evidence other than clinical trials
  - Usually, not more than a single confirmatory trial
  - Not evaluated in phases
    - May include feasibility and pilot studies
  - Fewer subjects
  - Shorter Duration
  - May order a Post approval study as a condition of approval

3

Pre-Approval Studies: Drugs/Therapeutic biologics

Pre-clinical: Preliminary efficacy, toxicity, and PK from in vivo and in vitro experiments

Phase 1: Drug cautiously given to small group of healthy volunteers (absorption, metabolism, excretion, early indications)

Phase 2: Beneficial and adverse effects, and dosing in a few hundred patients with the targeted condition

Phase 3: Comparative trials to determine benefit vs. harm involving thousands of patients. Intended for regulatory approval and marketing.

4

Limitations of Pre-marketing Clinical Trial Safety Evaluation

- Too small – can not identify rare events
- Too narrow –volunteers, no elderly, children, ethnicity, pregnancy
- Too limited –indication vs. off label use
- Too short – no events with a long latency period
- Ethically problematic at times to do RCT
- Expensive: time, effort, and money
- Generalizability limited by inclusions and exclusions

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Implication

- Insufficient information to fully characterize the safety profile
  - Rare and serious ADRs
  - Delayed /long latency effects
  - Drug/drug interactions etc
- Limited safety data for populations most likely to be future users (e.g: elderly, those with co-morbidities, concomitant drugs)
- No information on safety or effectiveness in pregnant, lactating women and children

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Sources of Post-market Safety Data

- Spontaneous case reports (Case Series)
- Registries
- Observational epidemiology studies
- Meta-analyses of observational studies
- Clinical trials
  - For new indications
  - For new doses
  - For new formulations
  - For safety studies
- Meta-analyses of clinical trials
  - Often based on a specific hypothesis

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Sources of Post-approval data (cont'd)

- Multiple data sources provide the basis for post-approval safety decision making
- No one source is adequate for all safety issues
- Multiple sources might not always tell you the same thing

8

Weight of Evidence

- Clinical Trials
- Epidemiology
- Spontaneous reports

Data from all sources are necessary to evaluate a drug's safety profile

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Devices: Post-approval Studies

- Section 205 of FDAMA 1997
  - Allowed effectiveness data to be collected post-approval
  - Does not apply to safety questions
  - Post-approval studies included among these post market controls
- Required as a Condition of Approval
  - Continued evaluation of effectiveness and reliability
  - Pediatric Studies
- Least Burdensome Provisions also apply to post-approval studies
- Types include: animal, laboratory, observational, or clinical studies

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Drugs/Therapeutic Biologics: Post-marketing Studies

- Accelerated approvals based on surrogate marker or animal efficacy data
  - Required post-marketing study to confirm clinical benefit
- Required Pediatric Studies of adult marketed drugs (unless deferred)

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Drugs/Therapeutic Biologics: Post-marketing Studies

- Required or agreed upon commitment
  - Clinical safety, efficacy, pharmacology, non-clinical toxicology
- Voluntary Studies
  - Chemistry, manufacturing, CMC, stability etc

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Post-marketing Studies

- Observational/epidemiological studies
  - Cohort
  - Case-control
  - Case-crossover
- Registries (most are exposure registries)
- Large Simple Trials
- Replicate findings using different study designs and populations

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Key Challenges of Observation Epidemiologic Database Studies

- Selecting Study Data base/study population and study design
- Measuring Exposures: Capturing Drug/biologic exposures and all other relevant exposures
- Measuring and accounting for Confounders
- Ascertaining all outcomes
- Selecting appropriate Controls

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Key Challenges of Registry

- Recruitment and retention
- Measuring all Exposures and Confounders
- Ascertaining all outcomes
- Selecting appropriate controls

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FDAAA
TITLE IX — ENHANCED AUTHORITIES REGARDING POSTMARKET SAFETY OF DRUGS

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Title IX – Subtitle A: Postmarket Studies and Surveillance

- New authorities to:
  - Require postmarket epidemiology studies and clinical trials
  - Require sponsors to make safety related labeling changes
  - Require sponsors to develop and comply with risk evaluation and mitigation strategies (REMS)

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Sec. 901- Post Market Studies and Surveillance

- FDA may require studies at the time of approval, or after approval based on new safety information and appropriate scientific data
- Requirement must be based on scientific data and is limited to certain specific purposes:
  - *To assess a known serious risk related to the use of the drug involved*
  - *To assess signals of serious risk related to the use of the drug*
  - *To identify an unexpected serious risk when available data indicates the potential for a serious risk*

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Post Market Studies and Surveillance

- Limited to Rx drugs and biologics; does not apply to OTC drugs and does not apply to generics
- Before requiring a study, must find that adverse event reporting and the active postmarket risk identification and analysis system (to be established under the Act) will not be sufficient to meet the purposes described previously
- Before requiring a clinical trial, must determine that a post approval study or studies (epidemiology) will not be sufficient

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Sec. 905 -Pharmacovigilance/ Active Surveillance

- Applies to drugs and biologics
- FDA must, through collaborations
  - develop methods to obtain access to disparate data sources; and
  - develop validated methods for the establishment of a risk identification and analysis system to link and analyze safety data from multiple sources
- Goals: system to include 25 million patients by 7/1/2010 and 100 million by 7/1/2012

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Back up Slides

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Comparison of Drugs and Medical Devices

Feature		Drugs	Devices
Development	Focus	Discovery	Design
	Mechanism of Action	Chemical and systemic	Physical and local
Regulation	Regulatory pathways	1	2
	Standard for safety and effectiveness	Well-controlled Phase III clinical trials	Based on degree of risk and regulatory pathway
	Number of required evaluation phases	3	Not generally evaluated in phases
	Number of clinical studies usually required for approval	1-2	1

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Comparison of Drugs and Medical Devices (con't)

Feature		Drugs	Devices
Evaluation Issues			
	Influence of skill of user	Low	High
	Product evolution	Low	High
	Number of companies	Small	Large
	Size of companies	Large	Small

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Summary of Breakout Sessions & Discussions

What have we learned:
Identifying the critical issues

Site Recruitment

- Return on Investment
  - Key is most influential person at site
  - Protocol/CRF requirements
  - Standard of care consideration
  - Publication Strategy
    - Class I evidence to support reimbursement
    - Site specific interest
- Product Interest
- Market Position – competing with novel technology or other studies enrolling the same patient population
- Balancing real world experience with center's selected for compliance
- How do we create interest?

IRB Opportunity

- Increased distribution/visibility of IRB letter
  - Content includes explanation on PAS and use of central of IRBs
- Outreach/education for IRBs regarding PAS
- Additional guidance for IRBs regarding review of PAS
  - Web information targeting IRBs
- IRB letter explaining reason and conditions of PAS created/approved along with PAS protocol
- Assesses fair market value to ensure no coercion
- IRB requirements to disclose investigator financial relationships in informed consent
- Use of centralized IRB
  - Useful when have multiple sites
  - More expeditious

Patient Recruitment – Study Elements

- Designing PAS with broad inclusion/exclusion criteria
  - All comers, off label, contraindicated
- Borrowing patients from the IDE study to support the PAS when possible
- Borrowing patients from the PAS to support the long term follow-up of the IDE study when possible
- Ability to be flexible in manner of collecting data
  - Using tools for remote data collection as much as possible
  - Accommodating snowbirds
- Focus group of independent clinicians to assess feasibility of PAS design

Patient Recruitment – Site Elements

- Most crucial element is research coordinator
- Site's relationship with patient
- Patient trust
- Research staff turnover rate
- Public Service Announcements encouraging patients to participate in study
- Web information regarding PAS
- No *a priori* reason why a patient cannot participate in more than one study
- Access to clinicians
- Targeting messages for the expanded population

Patient Recruitment – Sponsor Tips

- Training the investigator to promote/recruit for the study
  - ROI for investigator
  - Financial disclosure information on informed consent
- Showing the site their performance compared to other sites
- Screening logs
  - Help identify if inclusion/exclusion criteria require modification

Patient Retention

- Increase time windows for follow-up
- Classification of lost to follow-up
  - 2 missed visits in a row, are they really lost?
- Captive versus non-captive
- Unexpected factors
- Paying for patient's travel expenses or other study participation expenses
- Keeping patients informed of study progress along the way
- Access to clinicians

Summary

- Need for IRB education/guidance
- ROI for site, patient, sponsor
- Early collaboration between FDA/Industry on PAS design requirements
  - Better understanding of post approval objectives

ATTACHMENT G: Speaker Bios

Danica Marinac-Dabic, MD, PhD is a Director of the Division of Epidemiology at the Center for Devices and Radiological Health, Food and Drug Administration. She is a physician and epidemiologist with the background in obstetrics, gynecology and perinatal epidemiology. Dr. Marinac-Dabic leads three postmarket programs at CDRH:
(1) Post-Approval Studies Program, that encompasses the design, review, monitoring and oversight of the post-approval studies mandated as a condition of approval;
(2) Postmarket Surveillance Studies Program, in charge of postmarket studies mandated under Section 522 of the Act; and (3) Epidemiologic Research Program, designed to build medical device regulatory research infrastructure and conduct independent epidemiologic research studies to ensure CDRH science-based regulatory decision making. Dr. Marinac-Dabic serves as the Chair of the CDRH Human Subject Research Review Committee, the Chair of the CDRH Epidemiologic Research Council and the Member of the FDA Research Quality Assurance Board. Dr. Marinac-Dabic earned her M.D., Master of Science Degree in Human Reproduction and Ph.D. in Epidemiology from the University of Belgrade Medical School, Belgrade, Yugoslavia. Dr. Marinac-Dabic is the author of several book chapters, manuscripts and presentations on various topics in the field of medical device epidemiology and surveillance.

Dr. David Rutledge *is currently Director, Worldwide Clinical Affairs with Abbott Vascular. He brings 25 years experience as a clinical scientist possessing exceptional knowledge in protocol and eCRF development, scientific data analysis, integration of science with business needs, and developing international regulatory presentations and reports to agencies such as US FDA, China SFDA, Japan PMDA, EMEA, and CDSCO of India to name a few. He has extensive experience forming and directing teams that maintain strong relationships with local communities, corporations, professional associations, interdisciplinary medical and scientific professionals, and regulatory agencies. He has both management and professional experience on both pharmaceutical and device teams involving products within the cardiovascular, gastrointestinal, respiratory, and the AIDS therapeutic areas. As a former Professor and Chairman in academia, he understands the role of the role of a PI as a sponsor-investigator in clinical trials. He was inducted as a Fellow of the American Heart Association in 1995. His talk today will focus on industry's perspective on patient retention.*

Todd Fonseca has over 15 years of experience in the medical device industry. He has held a variety of positions in regulatory affairs, product reliability, and clinical research. He is currently a Clinical Research Senior Director in Medtronic's Neuromodulation Division.

Christine Pierre has been committed to human subject protection and clinical site operations for more than 20 years. She founded and is president of RxTrials Inc. RxTrials is an elite network of investigative sites that conduct in-patient and out-patient clinical research in a variety of therapeutic areas. RxTrials provides site support services, which include education, operational and clinical expertise. Recognizing the need for education for the research team, she created RxTrials Institute a non profit organization (status pending approval) offering training and education through both public and customized courses and is the host of the Site Solutions Summit, bringing together sites and industry stakeholders to identify and establish best clinical research site business practices. Christine was Chair of the Board of Trustees of the Association of Clinical Research Professionals and served on the board of trustees for 8 years. She has been the Sub Investigator of a multi-center clinical trial and Investigator of various single-center

studies. Christine frequently lectures, moderates panels and conducts workshops at national and international conferences and is on the editorial board of *Clinical Trials Advisor and eCliniqua and the board of advisors of Healogica* and the steering committee of the *Clinical Trials Transformation Initiative (CTTI).* She co-authored the book *Responsible Research: A Coordinators Guide* and has been nominated as one of the top female business professionals in Maryland.

Dr. Steven Pashko has been involved in clinical research since 1979. He received training as a Master's level experimental psychologist, a doctoral level CNS pharmacology and undertook re-specialization training in clinical psychology that lead to licensing as a psychologist. His work background has been in the evaluation of health care, having conducted extraordinarily diverse types of studies for drug, device and biotechnology companies. These have included epidemiological, medical claims, outcomes, pharmacoeconomic, registries and regulatory-compliant phase II, III and IV clinical trials. Dr Pashko has run more than 60 pharmaceutical clinical trials, conducted more than 40 clinically-oriented health care research studies, published 2 books, authored more than 30 published journal articles, written 25 major research reports and designed and implemented more than 10 full-scale health care programs.

Mr. Paul Goebel is President of Paul W Goebel Consulting, Inc., an independent consulting firm located in Monrovia, Maryland. He was formerly:

- Vice President of Chesapeake Research Review, an independent IRB in Columbia, Maryland;
- Senior Education Coordinator for the Office for Human Research Protections (OHRP);
- Associate Director for Human Subject Protection in the Office of the Commissioner, FDA (He coordinated FDA policy for protection of human subjects of research.);
- Chair of FDA's IRB; and
- Editor of the 1998 update of the FDA Information Sheets for Institutional Review Boards and Clinical Investigators.

Nancy Dianis is a registered nurse and education specialist with extensive experience in nursing management, operations, and clinical research. She is a Vice President and an Associate Director of Westat's Clinical Trials Area, with responsibility for commercial contract and select government contracts. She directs a broad range of projects, including epidemiologic studies and clinical trials for the National Institutes of Health (NIH) and the Centers for Disease Control and Prevention. She recently directed a large, strategically important study of NIH's clinical research networks, as part of the NIH Roadmap initiative. Before joining the Westat staff, Ms. Dianis was a director of nursing at Johns Hopkins Bayview Medical Center and the NIH Clinical Center. Ms. Dianis has been an adjunct instructor of nursing at the University of Maryland School of Nursing, the Johns Hopkins School of Nursing, the George Mason University School of Nursing, and the University of Rochester School of Nursing. She is a graduate of Illinois Wesleyan University and the University of Rochester.

Dr. Solomon Iyasu currently serves as Director, Division of Epidemiology, Office of Surveillance and Epidemiology, in the Center for Drug Evaluation and Research (CDER) of the US Food and Drug Administration. In this role, he directs the pharmaco-epidemiology program for drug safety. Dr. Iyasu joined the FDA's Division of Pediatric Drug Development, CDER in 2002 and served as a medical team leader and later as Acting Deputy Division Director until 2005. In this role, Dr. Iyasu led the review of post-marketing pediatric adverse events for 50 drugs and has coordinated and/or presented the safety reviews for public discussion during seven

Pediatric Advisory Committee meetings. Prior to joining the FDA in 2002, Dr. Iyasu worked as a Medical Epidemiologist at the Centers for Disease Control and Prevention (CDC) in Atlanta for almost 13 years. From 1995 to 2002, Dr. Iyasu served as the CDC liaison to the Committee on Fetus and Newborn, American Academy of Pediatrics. Dr. Iyasu was educated both in the United States and overseas. He completed his medical training and internship at the University of Delhi, India (1982), received his Master of Public Health training from Johns Hopkins University (1985). At the CDC, he completed fellowship training in Applied Epidemiology with the Epidemic Intelligence Service (1989-1991) and a Residency in Preventive Medicine (1990-1992) in Atlanta, Georgia.

John Smith's practice focuses primarily on assisting medical device companies in successfully addressing U.S. Food and Drug Administration (FDA) regulatory issues. A former associate professor at Massachusetts General Hospital/Harvard Medical School, John has extensive regulatory experience both in representing his clients at Hogan & Hartson and as the founding Director of the Regulatory Affairs Program at the Center for Integration of Medicine and Innovative Technology (CIMIT), a nonprofit consortium of the Harvard Medical Institutions and the Massachusetts Institute of Technology dedicated to medical product development. He has also served as a consultant to the Radiological Devices Panel of the Medical Devices Advisory Committee at FDA's Center for Devices and Radiological Health. In addition to his legal background, John has broad medical practice experience as a board certified, fellowship-trained musculoskeletal radiologist in both the academic and private practice settings, providing clinical care and taking part in clinical trials. John has written numerous articles on the regulatory issues surrounding new medical technology in both the medical and legal literature, and has been an invited speaker in a variety of industry, medical, academic, and government settings. John is active with a number of professional and nonprofit organizations, including the Radiological Society of North America, where he chairs the Committee on Resolutions and Bylaws and the American College of Radiology, where he is the former chair of the Safety Committee.

ATTACHMENT H: Breakout Session Questions

Patient Recruitment

1. What are the most important patient factors that pose a barrier to recruiting patients for post-approval studies?
    a. What are the patient factors that increase recruitment success?
    b. What are the patient factors that decrease recruitment success?
    c. Are there different patient factors in pre- and post approval studies?
        i. Do patients care about the science? How do patients perceive the pre-approval study requirements compared with the post approval study requirements?
        ii. Does this/How does this impact patient recruitment?

    What are some strategies that have been successful in overcoming a long term commitment?
    d. Do these factors vary by the type of site (academic, community, etc.)?
    e. Is there variation based on geography?
    f. Are they influenced by socio-economic factors?
    g. Are there different patient demographic factors affecting recruitment?
        i. Age
        ii. Sex
        iii. Race/ ethnicity

2. Does paying participants for time, travel, etc increase interest in participating?
    a. What should influence payment level?
    b. Is there a critical payment level?
    c. When considering all factors influencing patient participation, at what point are the cumulative benefits of participating in PAS coercion (at worst) or likely to introduce bias (at best)?
        i. Can this be determined up front, or how can it be detected after the fact?
    d. If payment isn't a key factor, what is the best incentive for patients to participate?

3. Do site compensation and the payment structure impact patient recruitment and/or patient retention?

4. Some patients in the pre-approval study are also followed as part of the post-approval study.
    a. What are the challenges of using the same patients in the pre-approval study as in the post-approval study?
    b. What are the pros and cons of consenting patients for long-term follow-up in the IDE phase?

Site Recruitment

5. Many PAS need to look at the real-world experience of a device in the post-market period. This would require sites that did not participate in the pre-market trial.
    a. What are the pros and cons of recruiting investigators who did not participate in the original pre-approval study?
        i. Sponsor's clinical/RA perspective, legal/contractual perspective
        ii. IRB and FDA perspective

iii. Site's perspective

b. How do you identify these sites?
c. What has worked in identifying sites?
d. What hasn't worked?
e. What are the barriers that sites state that prevent them from participating?
f. What additional support is needed for new sites?
g. What has worked well in getting these new sites up and running?
h. Once a site has participated in a PAS, can this site meet the criteria for a 'real-world' experience for a future PAS?

6. Many post-approval studies are conducted at multiple sites. Institutions may consider use of a central IRB review process given that "institutions involved in multi-institutional studies may use joint review, reliance upon the review of another qualified IRB, or similar arrangements aimed at avoidance of duplication of effort" (21 CFR 56.114, Cooperative Research)
    a. What are the pros and cons of using a centralized IRB?
    b. Are the IRB responsibilities of pre-approval studies fully applicable to PAS?
    c. Are the IRB considerations different for PAS than pre-approval studies?

<u>Patient Retention</u>

7. What is the most important factor that motivates patients to stay in a clinical trial?

8. What are some of the patient retention strategies that have been used and what are the pros and cons of these strategies?

9. Do pre- and post- approval studies have different factors that impact retention?
    a. Logistics (transportation, time off work, relocation)?
    b. Patient outcome?
    c. Access to care?
    d. Access to specialist?
    e. Payment for follow-up care?
    f. Assurance of payment for treatment of AEs?
    g. Insurance payments?

10. Do the retention factors vary depending on the method of follow-up?
    a. In-person, clinic visits
    b. Phone follow-up
    c. Mail or internet follow-up
    d. Remote monitoring

11. "Non-captive" patients (those with quality of life conditions, e.g., back pain) may be significantly less likely to continue long term follow up compared with "captive" patients (those with life threatening conditions, e.g., cardiac conditions) because they may be more likely to drop out when they get better.
    a. Since the motivation to participate is different, should this be taken into consideration when arriving at the type/amount of incentive to participate in long term follow up?

b. At what amount does an incentive become 'coercive' for each of these groups? Does payment structure, e.g., back loading, potentially improve retention or is it coercive?

Patient Compliance

12. For device trials many times we talk about retention equaling "not lost to follow-up". There are additional compliance issues that are also important.
    Treatment outcome can influence patient compliance/retention.
    a. Have you seen this phenomenon, what appears to drive this?
        1. Nature of the condition under study (e.g., life threatening vs. quality of life conditions).
        2. Litigation
        3. Relationship with Investigator/site staff
        4. Other
    b. What strategies have been used successfully to assure retention compliance?
    c. How do sponsors and FDA account for disproportionate follow-up so that it does not bias long term results/analyses?

13. With proposals to significantly extend duration of follow-up for patients who participated in a pre-approval study (for the purposes of PAS), what obstacles and opportunities are there for the logistics of implementing such follow up?

14. Many device trials are done only at large referral centers.

    a. Is there an issue following patients if the "site" is not close to the patient's home or the patient relocates?
        1. Patient perspective
        2. Site perspective
        3. IRB and FDA perspectives

    b. Are the issues the same if the patient was originally enrolled at a smaller enrolling site or 'community' type medical practice?
        1. Patient perspective
        2. Site perspective
        3. IRB and FDA perspectives
    c. What are options that can increase follow-up in these studies?
    d. What are the pros and cons of these options?
    e. Where can flexibility be built into study design, compliance and retention expectations for PAS that could positively impact follow-up in these studies?

Other Questions

15. Do sites that are the *top performers (recruitment, compliance, retention)* for pre-approval trials, also do well in PAS?
    a. What are the best site-specific predictors for good
        i. recruitment in PAS?
        ii. compliance
        iii. retention

16. What are the most important site factors that are related to high retention rates in a clinical trial?
    a. Are there different patient factors in pre- and post approval studies?
    b. Does site experience make a difference?
    c. Are there differences in academic vs. community/office based sites?

17. If a site is doing poorly in recruiting, what has helped to increase enrollment?
    a. What techniques have not been successful?
    b. Are these techniques similar or different for PAS vs. Pre-approval studies?

18. What role does site staffing play in recruiting patients?
    a. Experience of staff?
    b. Training or education of staff?
    c. The number of trials each coordinator is recruiting for?

19. What role does site staffing play in patient retention?
    a. Experience of staff?
    b. Training or education of staff?
    c. The number of trials each coordinator is responsible for?

20. What are the pros and cons of having a general site staff (trained on the protocol) conduct follow-up vs. having a dedicated person who does only follow-up?

21. Historically, when and how are retention expectations relayed to the sites and to patients? How have conditions of approval PAS affected this?
    a. What is working to maximize retention given changes in duration of follow-up

22. To track patients that may have died, how often is the National Death Registry used?
    a. What are the logistical issues?
    b. Are there patient privacy concerns?
    c. Can patient give consent to search the NDR at the time of enrollment?

23. Does the number of contacts, outside of in-person visits play a role in patient retention or recruitment?

24. Do tools such as newsletter, “birthday card” or other contact with patients increase follow-up rates?

ATTACHMENT I: Workshop Panel Questions

1. A CDRH Epidemiologist is a member of almost every PMA review team focused on identifying issues that may be appropriately addressed in a PAS should the device be approved. If the review process determines that there are questions that must be addressed in a PAS, it has become a Center goal to reach agreement with the sponsor on the full study protocol (or at least an outline) by the time of approval. This is to facilitate the immediate implementation of the study to avoid any surveillance "blind spots". We are not always successful in reaching agreement on the study protocol.

   What would you recommend that would help our study design negotiations with industry become more successful?

2. CDRH knows that collaboration among stakeholders will produce higher quality post approval studies. In addition to working with industry on study excellence, we think involvement from CRO's, professional societies, industry groups would add value.

   Please discuss ways that we might involve these stakeholders (as well as others you may think of) and what benefits or problems we might see as a result of this involvement

3. A PAS often requires long-term follow-up of the pivotal trial cohort.

   Please discuss the most important factors and strategies to ensure a smooth transition from premarket study to PAS, including informed consent and tracking mortality

4. A PAS often requires the enrollment of new patients.

   Please discuss the steps and strategies that must be in place to ensure successful enrollment of new patients

5. Obtaining IRB approval is a required first step in the implementation of a PAS.

   Please discuss the obstacles that an IRB may confront in granting approval and the impact these obstacles have. What can CDRH, industry, and the IRB do to make this process more efficient and effective?

6. A PAS is conducted in a "real world setting". Thus, a PAS will likely include a broader population of patients and providers than the premarket study.

   Please discuss the impact of including these broader populations on the implementation of PAS

7. A PAS will likely provide a wide range of data on long term device performance outcomes such as the effects of re-treatment and product change, sub-group outcomes, effectiveness of training, less common safety endpoints. A PAS may add some burden but it will offer some future benefit.

Please discuss the potential benefits of a PAS for new IDE studies for future generations of the device

8. The recommendation for a PAS often comes from the Advisory Panel.

   Please discuss the impact on PAS that panel members can have and the implications of the unique role